Access DB# 157940

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Andrew D. Kosar Examiner# : 80341 Date: 6/29/05

Art Unit: 1654 Phone Number: (571)272-0913 Serial Number: 10/817,248

Mail Box and Bldg/Room Location: **Mail: REM 3c18** Results Format Preferred (circle): **Paper** Disk E-mail
Office: REM 3c04

If more than one search is submitted, please prioritize searches in order of need. MJ

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Compounds and methods for treatment of thrombosis

Inventors (please provide full names): Sherin S. Abdel-Meguid; Robert E. Babine; Hongfeng Deng; Lei Jin; Jian Lin; Scott R. Magee; Harold V. Meyers; Pramod Pandey; Michael J. Rynkiewicz; David T. Weaver; Zihong Gho; Thomas D. Bannister

Earliest Priority Filing Date: 04/02/2003 (US PROV)

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the following:

100. A purified Factor XI protein or fragment thereof comprising a mutation, wherein said mutation is

(a) a mutation that enhances the ability of Factor XI catalytic domain to crystallize,

(b) a mutation of a residue that is otherwise post-translationally modified in an organism used for recombinant expression,

(c) a mutation that alters the charge of Factor XI,

(d) a mutation that eliminates a free, reactive sulfhydryl group of a cysteine,

(e) a combination of mutations that together alter the distribution of charge density without altering the overall charge of Factor XI,

(f) a mutation of the NH_2- or COOH-terminal residue of Factor XI, or

(g) a mutation that alters the folding of Factor XI.

wherein the mutation is:

(i) S434A;
(ii) T475A;
(iii) S434A, T475A;
(iv) S434A, T475A, K422A
(v) S434A, T475A, K437A;
(vi) S434A, T475A, K486A;
(vii) S434A, T475A, K505A;
(viii) S434A, T475A, K509A;
(ix) S434A, T475A, C482S;
(x) S434A, T475A, C482S, K437A;
(xi) S434A, T475A, C482S, R479A;
(xii) S434A, T475A, C482S, K505A;
(xiii) S434A, T475A, C482S, D476A;
(xiv) S434A, T475A, AVC-terminal trucation; or
(xv) S434A, T475A, C482S, Y416S.

****

STAFF USE ONLY

Searcher: _____
Searcher Phone: _____
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: _____
Searcher Prep & Review Time: _____
Clerical Prep Time: _____
Online Time: _____

Type of search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Full Text _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN _____
Dialog _____
Questel/Orbit _____
Dr. Link _____
Lexis/Nexis _____
Sequence System _____
WWW/Internet _____
Other (specify) _____

```
=> fil reg; d ide
FILE 'REGISTRY' ENTERED AT 14:15:37 ON 26 JUL 2005
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STRUCTURE FILE UPDATES:   25 JUL 2005  HIGHEST RN 856925-80-9
DICTIONARY FILE UPDATES:  25 JUL 2005  HIGHEST RN 856925-80-9

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html


L19  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   9013-55-2  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Blood-coagulation factor XI (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   AHF-C
CN   Antihemophilic C factor
CN   Antihemophilic factor C
CN   Blood-coagulation factor III, antecedent
CN   Blood-plasma thromboplastin antecedent
CN   Plasma thromboplastin antecedent
CN   PTA
CN   PTA (factor)
DR   9035-65-8
MF   Unspecified
CI   MAN
LC   STN Files:   AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,
       CANCERLIT, CAPLUS, CHEMCATS, EMBASE, IPA, MEDLINE, MRCK*, TOXCENTER,
       USPAT2, USPATFULL
         (*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
```

785 REFERENCES IN FILE CA (1907 TO DATE)
12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
785 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> => fil capl; d que l21
FILE 'CAPLUS' ENTERED AT 14:38:15 ON 26 JUL 2005
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FILE COVERS 1907 - 26 Jul 2005 VOL 143 ISS 5
FILE LAST UPDATED: 25 Jul 2005 (20050725/ED)

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This file contains CAS Registry Numbers for easy and accurate
substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L4	698	SEA FILE=CAPLUS ABB=ON	FACTOR XI/OBI
L5	1659	SEA FILE=CAPLUS ABB=ON	CATALYTIC?/OBI(2A)DOMAIN#/OBI
L6	269242	SEA FILE=CAPLUS ABB=ON	CRYSTALLI?/OBI
L7	220829	SEA FILE=CAPLUS ABB=ON	CHARGE#/OBI
L8	12612	SEA FILE=CAPLUS ABB=ON	SULFHYDRYL/OBI
L9	53481	SEA FILE=CAPLUS ABB=ON	(N/OBI OR NH2/OBI OR AMINO/OBI OR COOH/OBI OR CARBOXY/OBI OR C/OBI)(2A)(TERMIN?/OBI OR END/OBI)
L10	13133	SEA FILE=CAPLUS ABB=ON	PROTEIN FOLDING/CT
L17	263445	SEA FILE=CAPLUS ABB=ON	MUTA?/OBI
L19	1	SEA FILE=REGISTRY ABB=ON	9013-55-2
L20	785	SEA FILE=CAPLUS ABB=ON	L19
L21	11	SEA FILE=CAPLUS ABB=ON	(L4 OR L20) AND L17 AND (L5 OR L6 OR L7 OR L8 OR L9 OR L10)

=> fil medl; d que l34

FILE 'MEDLINE' ENTERED AT 14:38:15 ON 26 JUL 2005

FILE LAST UPDATED: 23 JUL 2005 (20050723/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP
RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
L22          776 SEA FILE=MEDLINE ABB=ON  FACTOR XI/CT
L23        10335 SEA FILE=MEDLINE ABB=ON  CATALYTIC DOMAIN#
L24        66484 SEA FILE=MEDLINE ABB=ON  CRYSTALLI?
L25       291959 SEA FILE=MEDLINE ABB=ON  RECOMB?
L26        29513 SEA FILE=MEDLINE ABB=ON  SULFHYDRYL OR SULPHYDRYL
L27        62211 SEA FILE=MEDLINE ABB=ON  CYSTEINE
L28        79025 SEA FILE=MEDLINE ABB=ON  CHARGE#
L29       150646 SEA FILE=MEDLINE ABB=ON  (N OR NH2 OR AMINO OR COOH OR CARBOXY
                 OR C)(2A)(TERMIN? OR END)
L30        17497 SEA FILE=MEDLINE ABB=ON  PROTEIN FOLDING/CT
L31       349176 SEA FILE=MEDLINE ABB=ON  MUTATION+NT/CT
L33           75 SEA FILE=MEDLINE ABB=ON  L22(L)GE/CT
L34            9 SEA FILE=MEDLINE ABB=ON  L33 AND L31 AND (L23 OR L24 OR L25 OR
                 L26 OR L27 OR L28 OR L29 OR L30)
```

GE = genetics subheading

=> fil embase; d que l46; d que l49

FILE 'EMBASE' ENTERED AT 14:38:16 ON 26 JUL 2005

FILE COVERS 1974 TO 21 Jul 2005 (20050721/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
L35          952 SEA FILE=EMBASE ABB=ON  BLOOD CLOTTING FACTOR 11/CT
L36       283536 SEA FILE=EMBASE ABB=ON  MUTATION+NT/CT
L37         5487 SEA FILE=EMBASE ABB=ON  CATALYTIC DOMAIN#
L38        34732 SEA FILE=EMBASE ABB=ON  CRYSTALLI?
L39       195282 SEA FILE=EMBASE ABB=ON  RECOMB?
L40        10337 SEA FILE=EMBASE ABB=ON  SULFHYDRYL OR SULPHYDRYL
L41        47196 SEA FILE=EMBASE ABB=ON  CYSTEINE
L42        68461 SEA FILE=EMBASE ABB=ON  CHARGE#
L43       142113 SEA FILE=EMBASE ABB=ON  (N OR NH2 OR AMINO OR COOH OR CARBOXY
                 OR C)(2A)(TERMIN? OR END)
L44        23189 SEA FILE=EMBASE ABB=ON  PROTEIN FOLDING/CT
L46            5 SEA FILE=EMBASE ABB=ON  L35/MAJ AND L36/MAJ AND (L37 OR L38 OR
                 L39 OR L40 OR L41 OR L42 OR L43 OR L44)
```

```
L35          952 SEA FILE=EMBASE ABB=ON  BLOOD CLOTTING FACTOR 11/CT
L36       283536 SEA FILE=EMBASE ABB=ON  MUTATION+NT/CT
L37         5487 SEA FILE=EMBASE ABB=ON  CATALYTIC DOMAIN#
L38        34732 SEA FILE=EMBASE ABB=ON  CRYSTALLI?
L39       195282 SEA FILE=EMBASE ABB=ON  RECOMB?
```

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L40        10337 SEA FILE=EMBASE ABB=ON  SULFHYDRYL OR SULPHYDRYL
L41        47196 SEA FILE=EMBASE ABB=ON  CYSTEINE
L42        68461 SEA FILE=EMBASE ABB=ON  CHARGE#
L43       142113 SEA FILE=EMBASE ABB=ON  (N OR NH2 OR AMINO OR COOH OR CARBOXY
                 OR C)(2A)(TERMIN? OR END)
L44        23189 SEA FILE=EMBASE ABB=ON  PROTEIN FOLDING/CT
L47        30083 SEA FILE=EMBASE ABB=ON  AMINO ACID SUBSTITUTION/CT
L48        55419 SEA FILE=EMBASE ABB=ON  PROTEIN STRUCTURE/CT
L49            8 SEA FILE=EMBASE ABB=ON  L35 AND L36 AND L47 AND ((L37 OR L38
                 OR L39 OR L40 OR L41 OR L42 OR L43 OR L44) OR L48)


=> s l46 or l49

L75           11 L46 OR L49

=> fil PASCAL, BIOTECHNO, ESBIOBASE, BIOSIS, CONFSCI, BIOTECHDS, DISSABS,wpids

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=> d que l63; d que l65; d que l72

L50         2615 SEA FACTOR(W)(XI OR 11)
L51      1347005 SEA MUTA?
L53       452523 SEA CRYSTALLI?
L61          349 SEA L50 AND L51
L63            4 SEA L61 AND L53



L50         2615 SEA FACTOR(W)(XI OR 11)
L51      1347005 SEA MUTA?
L55        29423 SEA SULFHYDRYL OR SULPHYDRYL
L61          349 SEA L50 AND L51
L65            2 SEA L61 AND L55
```

```
L50        2615 SEA FACTOR(W)(XI OR 11)
L51     1347005 SEA MUTA?
L52       20342 SEA CATALYTIC?(2A) DOMAIN#
L54      762450 SEA RECOMB?
L56      138934 SEA CYSTEINE
L57      831908 SEA CHARGE#
L58      440145 SEA (N OR NH2 OR AMINO OR COOH OR CARBOXY OR C)(2A)(TERMIN? OR
                END)
L59      870620 SEA FOLD###
L72          30 SEA L50(8A) L51 (S) (L52 OR L54 OR (L56 OR L57 OR L58 OR L59))


=> s l63 or l65 or l72

L76          32 L63 OR L65 OR L72

=> dup rem l34,l21,l75,l76
FILE 'MEDLINE' ENTERED AT 14:38:36 ON 26 JUL 2005

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PROCESSING COMPLETED FOR L34
PROCESSING COMPLETED FOR L21
PROCESSING COMPLETED FOR L75
PROCESSING COMPLETED FOR L76
L77          32 DUP REM L34 L21 L75 L76 (31 DUPLICATES REMOVED)
                ANSWERS '1-9' FROM FILE MEDLINE
                ANSWERS '10-20' FROM FILE CAPLUS
                ANSWERS '21-25' FROM FILE EMBASE
                ANSWERS '26-30' FROM FILE BIOTECHNO
                ANSWERS '31-32' FROM FILE ESBIOBASE

=> d iall 1-9; d ibib ed abs hitind 10-20; d iall 21-32; fil hom
```

L77 ANSWER 1 OF 32 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004495289 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15226185
TITLE: An Alu-mediated 31.5-kb deletion as the cause of factor XI deficiency in 2 unrelated patients.
AUTHOR: Mitchell Michael; Dai Letian; Savidge Geoffrey; Alhaq Anwar
CORPORATE SOURCE: Centre for Haemostasis and Thrombosis, The Haemophilia Reference Centre, 1st Floor North Wing, St Thomas' Hospital, London SE1 7EH United Kingdom..
Mike.Mitchell@gstt.sthames.nhs.uk
SOURCE: Blood, (2004 Oct 15) 104 (8) 2394-6. Electronic Publication: 2004-06-29.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 20041007
Last Updated on STN: 20041219
Entered Medline: 20041123

ABSTRACT:
Factor XI deficiency (MIM 264900) is an autosomal bleeding disorder of variable severity. Inheritance is not completely recessive as heterozygotes may display a distinct, if mild, bleeding tendency. Recent studies have shown the causative mutations of factor XI deficiency, outside the Ashkenazi Jewish population, to be highly heterogeneous. We studied 39 consecutively referred patients with factor XI deficiency to identify the molecular defect. Conventional mutation screening failed to identify a causative mutation in 4 of the 39 patients. Epstein-Barr virus (EBV)-transformed cells from these 4 patients were converted from a diploid to haploid chromosome complement. Subsequent analysis showed that 2 of the patients had a large deletion, which was masked in the heterozygous state by the presence of a normal allele. We report here the first confirmed whole gene deletion as the causative mutation of factor XI deficiency, the result of unequal homologous **recombination** between flanking Alu repeat sequences.

CONTROLLED TERM: *Alu Elements: GE, genetics
Base Sequence
***Factor XI: GE, genetics**
***Gene Deletion**
Humans
Molecular Sequence Data
CAS REGISTRY NO.: 9013-55-2 (Factor XI)

L77 ANSWER 2 OF 32 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2004488544 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15456490
TITLE: Severe factor XI deficiency caused by a Gly555 to Glu mutation (factor XI-Glu555): a cross-reactive material positive variant defective in factor IX activation.
AUTHOR: Zivelin A; Ogawa T; Bulvik S; Landau M; Toomey J R; Lane J; Seligsohn U; Gailani D
CORPORATE SOURCE: Amalia Biron Research Institute of Thrombosis and Hemostasis, Chaim Sheba Medical Center, Tel Hashomer, Israel.
CONTRACT NUMBER: HL58837 (NHLBI)
SOURCE: Journal of thrombosis and haemostasis : JTH, (2004 Oct) 2 (10) 1782-9.
Journal code: 101170508. ISSN: 1538-7933.

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200507
ENTRY DATE: Entered STN: 20041001
Last Updated on STN: 20050722
Entered Medline: 20050721

ABSTRACT:
During normal hemostasis, the coagulation protease factor (F)XIa activates FIX. Hereditary deficiency of the FXIa precursor, FXI, is usually associated with reduced FXI protein in plasma, and circulating dysfunctional FXI variants are rare. We identified a patient with < 1% normal plasma FXI activity and normal levels of FXI antigen, who is homozygous for a FXI Gly555 to Glu substitution. Gly555 is two **amino** acids **N-terminal** to the protease active site serine residue, and is highly conserved among serine proteases. **Recombinant** FXI-Glu555 is activated normally by FXIIa and thrombin, and FXIa-Glu555 binds activated factor IX similarly to wild type FXIa (FXIa(WT)). When compared with FXIa(WT), FXIa-Glu555 activates factor IX at a greatly reduced rate (approximately 400-fold), and is resistant to inhibition by antithrombin. Interestingly, FXIa(WT) and FXIa-Glu555 cleave the small tripeptide substrate S-2366 with comparable k(cat)s. Modeling indicates that the side chain of Glu555 significantly alters the electrostatic **charge** around the active site, and would sterically interfere with the interaction between the FXIa S2' site and the P2' residues on factor IX and antithrombin. FXI-Glu555 is the first reported example of a naturally occurring FXI variant with a significant defect in FIX activation.

CONTROLLED TERM: Antithrombin III: PD, pharmacology
Binding Sites
Electrostatics
*Factor IX: ME, metabolism
Factor XI: AN, analysis
Factor XI: GE, genetics
Factor XI: ME, metabolism
*Factor XI Deficiency: GE, genetics
Homozygote
Humans
Kinetics
Models, Molecular
***Mutation, Missense**
Protein Binding: GE, genetics
Research Support, N.I.H., Extramural
Research Support, U.S. Gov't, P.H.S.

CAS REGISTRY NO.: 9000-94-6 (Antithrombin III); 9001-28-9 (Factor IX); 9013-55-2 (Factor XI)

L77 ANSWER 3 OF 32 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2002164038 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11895778
TITLE: Factor XI deficiency in French Basques is caused predominantly by an ancestral Cys38Arg mutation in the factor XI gene.
AUTHOR: Zivelin Ariella; Bauduer Frederic; Ducout Louis; Peretz Hava; Rosenberg Nurit; Yatuv Rivka; Seligsohn Uri
CORPORATE SOURCE: Institute of Thrombosis and Hemostasis, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel.
SOURCE: Blood, (2002 Apr 1) 99 (7) 2448-54.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020317
Last Updated on STN: 20020503
Entered Medline: 20020502

ABSTRACT:
Inherited factor XI deficiency is an injury-related bleeding disorder that is rare in most populations except for Jews, in whom 2 mutations, a stop mutation in exon 5 (type II) and a missense mutation in exon 9 (type III), predominate. Recently, a cluster of 39 factor XI-deficient patients was described in the Basque population of Southwestern France. In this study, we determined the molecular basis of factor XI deficiency in 16 patients belonging to 12 unrelated families of French Basque origin. In 8 families, a nucleotide 209T>C transition in exon 3 was detected that predicts a Cys38Arg substitution. Four additional novel mutations in the factor XI gene, Cys237Tyr, Tyr493His, codon 285delG, and IVS6 + 3A>G, were identified in 4 families. Expression studies showed that Cys38Arg and Cys237Tyr factor XI were produced in transfected baby hamster kidney cells, but their secretion was impaired. Cells transfected with Tyr493His contained reduced amounts of factor XI and displayed decreased secretion. A survey of 206 French Basque controls for Cys38Arg revealed that the prevalence of the mutant allele was 0.005. Haplotype analysis based on the study of 10 intragenic polymorphisms was consistent with a common ancestry (a founder effect) for the Cys38Arg mutation.

CONTROLLED TERM: Check Tags: Male
Adolescent
Adult
Amino Acid Substitution
Animals
Arginine
Blotting, Western
Cell Line
Child
Child, Preschool
Cysteine
DNA: BL, blood
DNA: GE, genetics
Ethnic Groups: GE, genetics
***Factor XI: GE, genetics**
Factor XI: ME, metabolism
*Factor XI Deficiency: GE, genetics
France
Hamsters
Humans
Kidney
Middle Aged
***Mutation, Missense**
Polymerase Chain Reaction
*Polymorphism, Genetic
Recombinant Proteins: ME, metabolism
Transfection

CAS REGISTRY NO.: **52-90-4 (Cysteine)**; 74-79-3 (Arginine); 9007-49-2 (DNA); 9013-55-2 (Factor XI)
CHEMICAL NAME: 0 (**Recombinant** Proteins)

L77 ANSWER 4 OF 32 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 95195217 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7888672
TITLE: Six point mutations that cause factor XI deficiency.
AUTHOR: Pugh R E; McVey J H; Tuddenham E G; Hancock J F

CORPORATE SOURCE: Department of Academic Haematology, Royal Free Hospital Medical School, London, UK.
SOURCE: Blood, (1995 Mar 15) 85 (6) 1509-16.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950427
Last Updated on STN: 19950427
Entered Medline: 19950414

ABSTRACT:
We have identified six novel types of mutation that cause factor XI deficiency, an inherited bleeding disorder. Two are point mutations that interfere with the normal splicing of exons in the mRNA and four are point mutations that result in amino acid substitutions. One of these amino acid substitutions (Asp 16-->His) is near the **amino terminal end** of the protein. The other three amino acid substitutions (Leu 302-->Pro, Thr 304-->Ile, and Glu 323-->Lys) are in the fourth apple domain, a region that mediates dimerization of identical subunits of factor XI. All four amino acid substitutions cause a reduction in the amount of factor XI secreted from cells grown in vitro.

CONTROLLED TERM: Amino Acid Sequence
Base Sequence
Cells, Cultured
***Factor XI: GE, genetics**
*Factor XI Deficiency: GE, genetics
Humans
Molecular Sequence Data
***Point Mutation**
CAS REGISTRY NO.: 9013-55-2 (Factor XI)

L77 ANSWER 5 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2004510239 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15479396
TITLE: New observations on factor XI deficiency.
AUTHOR: Salomon O; Seligsohn U
CORPORATE SOURCE: Amalia Biron Research Institute of Thrombosis and Hemostasis, Chaim Sheba Medical Center, Tel Hashomer, Israel.. ophiras@sheba.health.gov.il
SOURCE: Haemophilia : official journal of the World Federation of Hemophilia, (2004 Oct) 10 Suppl 4 184-7.
Journal code: 9442916. ISSN: 1351-8216.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 20041014
Last Updated on STN: 20050420
Entered Medline: 20050419

ABSTRACT:
Factor (F) XI is an injury-related bleeding tendency that commonly occurs when trauma involves tissues rich in fibronolytic activators. Severe FXI deficiency is defined when the activity of FXI in plasma is less than 15 U dL(-1). The disorder is inherited as an autosomal recessive trait manifesting in homozygotes or compound heterozygotes, and infrequently in heterozygotes. So far 53 mutations in the gene of FXI have been described and four of them were found to be prevalent in Ashkenazi Jews, Iraqi Jews, Basques or the English

population. For each of the four mutations a founder effect was discerned. Inhibitors can develop in patients with FXI level < 1U dL(-1) who were exposed to plasma which seriously complicates their management during surgery. No correction of a prolonged aPTT by normal plasma is indicative of the presence of an inhibitor. In contrast to patients with haemophilia A, severe FXI deficiency provides no protection against myocardial infarction. In patients with severe FXI deficiency undergoing surgery, fresh frozen plasma is the treatment of choice. FXI concentrates can also be used but cause thrombosis in approximately 10% of patients, particularly those with cardiovascular disease. ***Recombinant*** FVIIa has successfully prevented bleeding during or after surgery in patients with FXI inhibitors.

CONTROLLED TERM: Blood Loss, Surgical: PC, prevention & control
Factor XI: AN, analysis
Factor XI: AI, antagonists & inhibitors
Factor XI: GE, genetics
*Factor XI Deficiency: CO, complications
Hemorrhage: ET, etiology
Hemorrhage: PC, prevention & control
Humans
Mutation
Recombinant Proteins: AN, analysis
Recombinant Proteins: AI, antagonists & inhibitors
Thrombosis: ET, etiology

CAS REGISTRY NO.: 9013-55-2 (Factor XI)
CHEMICAL NAME: 0 (**Recombinant** Proteins)

L77 ANSWER 6 OF 32 MEDLINE on STN
ACCESSION NUMBER: 1999030384 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9813019
TITLE: Characterization of a heparin binding site on the heavy chain of factor XI.
AUTHOR: Zhao M; Abdel-Razek T; Sun M F; Gailani D
CORPORATE SOURCE: Departments of Pathology and Medicine, Vanderbilt University, Nashville, Tennessee 37232, USA.
CONTRACT NUMBER: HL02917 (NHLBI)
HL58837 (NHLBI)
SOURCE: Journal of biological chemistry, (1998 Nov 20) 273 (47) 31153-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981221

ABSTRACT:
The glycosaminoglycan heparin enhances several reactions involving coagulation factor XI (FXI) including activation of FXI by factor XIIa, thrombin, and autoactivation; and inactivation of activated FXI (FXIa) by serine protease inhibitors. We examined the effect of heparin on inhibition of FXIa by the inhibitors C1-inhibitor (C1-INH) and antithrombin III (ATIII). Second order rate constants for inhibition in the absence of heparin were 1.57 x 10(3) and 0.91 x 10(3) M-1 s-1 for C1-INH and ATIII, respectively. Therapeutic heparin concentrations (0.1-1.0 units/ml) enhanced inhibition by ATIII 20-55-fold compared with 0.1-7.0-fold for C1-INH. For both inhibitors, the effect of heparin over a wide range of concentrations (10(-1) to 10(5) units/ml) produced bell-shaped curves, demonstrating that inhibition occurs by a template mechanism requiring both inhibitor and protease to bind to heparin. This

implies that FXI/XIa contains structural elements that interact with heparin. Human FXI contains a sequence of amino acids (R250-I-K-K-S-K) in the apple 3 domain of the heavy chain that binds heparin (Ho, D., Badellino, K., Baglia, F., and Walsh, P. (1998) J. Biol. Chemical 273, 16382-16390). To determine the importance of this sequence to heparin-mediated reactions, **recombinant** FXI molecules with alanine substitutions for basic amino acids were expressed in 293 fibroblasts, and tested in heparin-dependent assays. Inhibition of FXIa by ATIII in the presence of heparin was decreased 4-fold by alanine substitution at Lys253 (A253), with smaller effects noted for mutants A255 and A252. FXI undergoes autoactivation to FXIa in the presence of heparin. The rate of autoactivation was decreased substantially for A253 with modest decreases for A255 and A252. Substituting all four **charged** residues in the sequence resulted in a profound decrease in autoactivation, significantly greater than for any single substitution. Relative affinity for heparin was tested by determining the concentration of NaCl required to elute FXIa from heparin-Sepharose. Wild type FXIa eluted from the column at 320 mM NaCl, whereas FXIa with multiple substitutions (A252-254 or A250-255) eluted at 230 mM NaCl. All proteins with single substitutions in **charged** amino acids eluted at intermediate NaCl concentrations. The data indicate that FXI/XIa must bind to heparin for optimal inhibition by ATIII and for autoactivation. Lys253 is the most important amino acid involved in binding, and Lys255 and Lys252 also have roles in interactions with heparin.

CONTROLLED TERM: Alanine
Amino Acids, Diamino
Antithrombin III: PD, pharmacology
Binding Sites
Chromatography, Affinity
Complement 1 Inactivators: PD, pharmacology
Enzyme Activation
Factor XI: GE, genetics
*Factor XI: ME, metabolism
Factor XIa: GE, genetics
Factor XIa: ME, metabolism
Glutamic Acid
*Heparin: ME, metabolism
Mutation
Recombinant Proteins: ME, metabolism
Research Support, U.S. Gov't, P.H.S.
Sepharose: AA, analogs & derivatives
Sepharose: ME, metabolism

CAS REGISTRY NO.: 56-41-7 (Alanine); 56-86-0 (Glutamic Acid); 9000-94-6 (Antithrombin III); 9005-49-6 (Heparin); 9012-36-6 (Sepharose); 9013-55-2 (Factor XI)

CHEMICAL NAME: 0 (Amino Acids, Diamino); 0 (C1-inhibitor protein); 0 (Complement 1 Inactivators); 0 (**Recombinant** Proteins); 0 (heparin-sepharose); EC 3.4.21.27 (Factor XIa)

L77 ANSWER 7 OF 32 MEDLINE on STN

ACCESSION NUMBER: 1999005359 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9787168

TITLE: Identification of mutations and polymorphisms in the factor XI genes of an African American family by dideoxyfingerprinting.

COMMENT: Erratum in: Blood 1999 Mar 1;93(5):1786

AUTHOR: Martincic D; Zimmerman S A; Ware R E; Sun M F; Whitlock J A; Gailani D

CORPORATE SOURCE: Department of Pediatrics, Pathology, and Medicine, Vanderbilt University, Nashville, TN, USA.

CONTRACT NUMBER: HL02917 (NHLBI)
HL58837 (NHLBI)

SOURCE: Blood, (1998 Nov 1) 92 (9) 3309-17.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981130

ABSTRACT:
Congenital deficiency of factor XI is a rare condition associated with a mild to moderate bleeding diathesis that is most commonly found in persons of Jewish ancestry. The disorder has been reported sporadically in a number of other ethnic groups, but rarely in the black population. We report on the genetic analysis of the factor XI genes of two African American patients: a 9-year-old boy (the propositus) with mild factor XI deficiency and his mother. Both individuals have lifelong histories of excessive bleeding. Dideoxyfingerprinting, a technique combining components of single-strand conformational polymorphism analysis and dideoxy-chain termination sequencing, was used in the analysis. Both patients were found to be heterozygous for a mutation changing serine 248 to asparagine [corrected], whereas the propositus was heterozygous for an additional mutation on the paternal allele changing glutamine 226 to arginine. Both mutations reside in the third apple domain of the factor XI heavy chain, an area that has been shown to contain binding sites for factor IX, platelets, and glycosaminoglycans. Previously reported mutations in the factor XI gene seem to cause deficiency primarily by reducing protein expression. Because both alleles in the propositus contain amino acid substitutions, the significant amount of circulating factor XI in his plasma must be comprised entirely of abnormal molecules. Factor XI circulates as a homodimer, and the presence of mutations in both alleles of the factor XI gene suggests that his bleeding disorder is caused in part by the effect of the two abnormal gene products forming dimers in different combinations. Three neutral (not associated with amino acid changes) DNA polymorphisms were also identified in the two subjects: a C to T change at nucleotide 472 in exon 5, A to G at nucleotide 844 in exon 8, and T to C at nucleotide 1234 in exon 11. Analysis of a random sample of normal volunteers showed that these polymorphisms are relatively common, with allele frequencies of 7.4%, 19%, and 18%, respectively. This suggests that there is considerable genetic heterogeneity in the factor XI gene.

CONTROLLED TERM: Check Tags: Female; Male
Adult
*African Continental Ancestry Group: GE, genetics
Alleles
Amino Acid Substitution
Cells, Cultured
Child
DNA Fingerprinting
DNA Mutational Analysis
Dideoxynucleosides
Dimerization
Exons: GE, genetics
***Factor XI: GE, genetics**
Factor XI Deficiency: EH, ethnology
*Factor XI Deficiency: GE, genetics
Genetic Predisposition to Disease
Hemorrhagic Disorders: ET, etiology
Heterozygote

Humans
*Mutation, Missense
Polymorphism, Single-Stranded Conformational
Recombinant Fusion Proteins: ME, metabolism
Research Support, U.S. Gov't, P.H.S.
CAS REGISTRY NO.: 9013-55-2 (Factor XI)
CHEMICAL NAME: 0 (Dideoxynucleosides); 0 (Recombinant Fusion Proteins)

L77 ANSWER 8 OF 32 MEDLINE on STN
ACCESSION NUMBER: 94266778 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8206894
TITLE: Plasminogen mutants activated by thrombin. Potential thrombus-selective thrombolytic agents.
AUTHOR: Dawson K M; Cook A; Devine J M; Edwards R M; Hunter M G; Raper R H; Roberts G
CORPORATE SOURCE: British Bio-technology Ltd, Oxford, United Kingdom.
SOURCE: Journal of biological chemistry, (1994 Jun 10) 269 (23) 15989-92.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940721
Last Updated on STN: 19940721
Entered Medline: 19940713

ABSTRACT:
Plasmin, the enzyme responsible for degradation of fibrin in blood clots and thus thrombolysis, is normally formed when its zymogen plasminogen is activated by cleavage of the Arg561-Val562 bond by specific plasminogen activators. We have altered the activation characteristics of plasminogen by substituting the P3, P2, and P1' cleavage site residues with sequences from thrombin-cleavable proteins to produce a novel thrombolytic agent which instead is activated by the blood clotting system. Plasminogen variants with thrombin cleavage sites from fibrinogen, the thrombin receptor, factor XIII, and factor XI were cleaved by thrombin with times to 50% cleavage of 28 h, 2.5 h, 5.7 min, and 3 min, respectively. In vitro clot lysis studies have shown that a variant in which the P3-P1' residues of plasminogen were substituted by the P7-P1' residues (Thr363-Ile370) from factor XI (T51) was sufficiently rapidly cleaved by thrombin to be activated by the endogenous thrombin produced by the coagulation cascade, resulting in rapid clot dissolution. Thrombin-activatable plasminogen therefore has the capacity to short circuit the physiological hemostatic mechanisms and produce fibrinolytic activity localized to the site of thrombin formation, that is, at the thrombus itself. The novel activation mechanism combined with the natural long circulating half-life of plasminogen gives this type of thrombolytic agent the potential for thrombus-selective plasmin generation and an extended duration of action.

CONTROLLED TERM: Check Tags: Comparative Study
Amino Acid Sequence
Base Sequence
Enzyme Activation
Factor XI: GE, genetics
Factor XIII: GE, genetics
Fibrinogen: GE, genetics
*Fibrinolytic Agents: ME, metabolism
Humans
Molecular Sequence Data
Mutation

Searched by Barb O'Bryen, STIC 2-2518

*Plasmin: BI, biosynthesis
Plasminogen: GE, genetics
*Plasminogen: ME, metabolism
Protein Processing, Post-Translational
Receptors, Thrombin: GE, genetics
Recombinant Proteins: ME, metabolism
*Thrombin: ME, metabolism

CAS REGISTRY NO.: 9001-32-5 (Fibrinogen); 9001-91-6 (Plasminogen); 9013-55-2 (Factor XI); 9013-56-3 (Factor XIII)

CHEMICAL NAME: 0 (Fibrinolytic Agents); 0 (Receptors, Thrombin); 0 (**Recombinant** Proteins); EC 3.4.21.5 (Thrombin); EC 3.4.21.7 (Plasmin)

L77 ANSWER 9 OF 32 MEDLINE on STN

ACCESSION NUMBER: 92190478 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1547342

TITLE: Expression of human blood coagulation factor XI: characterization of the defect in factor XI type III deficiency.

AUTHOR: Meijers J C; Davie E W; Chung D W

CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle 98195.

CONTRACT NUMBER: HL16919 (NHLBI)

SOURCE: Blood, (1992 Mar 15) 79 (6) 1435-40.
Journal code: 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199204

ENTRY DATE: Entered STN: 19920509
Last Updated on STN: 19920509
Entered Medline: 19920417

ABSTRACT:
Human factor XI (FXI) is a blood coagulation factor participating in the early phase of the intrinsic pathway of blood coagulation. It circulates in blood as a glycoprotein composed of two identical chains held together by a single disulfide bond between the fourth apple domains. FXI has been expressed in baby hamster kidney (BHK) cells, where it was synthesized as a single-chain molecule that was converted to the dimer before secretion. The ***recombinant*** protein was fully active in a clotting assay, indicating that it interacted readily with other components of the coagulation cascade. A mutant FXI in which Phe283 was converted to Leu (Phe283Leu) was also expressed in BHK cells. This amino acid change occurs in the fourth apple domain of FXI and corresponds to the type III deficiency in Ashkenazi Jews. The mutant protein was secreted at reduced levels (about 8%) compared with normal FXI. This was due to a defect in the dimerization of the molecule rather than a decrease in the transcription of type III messenger RNA. Once secreted, however, the mutant protein consisted of a dimer with full biologic activity. The in vitro expression of FXI indicated that the impaired dimerization and secretion of the Phe283Leu mutant can account for the defect found in patients who are homozygous for the type III FXI deficiency.

CONTROLLED TERM: Amino Acid Sequence
Animals
Cell Line
*Factor XI: BI, biosynthesis
Factor XI: GE, genetics
*Factor XI Deficiency: BL, blood
Hamsters
Humans

Molecular Sequence Data
Mutation
***Recombinant Proteins: BI, biosynthesis**
Research Support, U.S. Gov't, P.H.S.
CAS REGISTRY NO.: 9013-55-2 (Factor XI)
CHEMICAL NAME: 0 (**Recombinant** Proteins)

L77 ANSWER 10 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:1033547 CAPLUS
DOCUMENT NUMBER: 142:19250
TITLE: Crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compounds for treatment of thrombosis
INVENTOR(S): Abdel-Meguid, Sherin S.; Babine, Robert E.; Deng, Hongfeng; Jin, Lei; Lin, Jian; Magee, Scott R.; Meyers, Harold V.; Pandey, Pramod; Rynkiewicz, Michael J.; Weaver, David T.
PATENT ASSIGNEE(S): Suntory Pharmaceutical Research Laboratories Llc, USA
SOURCE: PCT Int. Appl., 925 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004103270	A2	20041202	WO 2004-US10349	20040402
WO 2004103270	A3	20050512		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005143317	A1	20050630	US 2004-817248	20040402

PRIORITY APPLN. INFO.: US 2003-459910P P 20030402
OTHER SOURCE(S): MARPAT 142:19250
ED Entered STN: 02 Dec 2004
AB The present invention provides compds. that inhibit blood coagulation factor XIa and methods of preventing or treating undesired thrombosis by administering a compound of the invention to a mammal. To facilitate the identification and/or design of high affinity inhibitors for factor XIa, several three-dimensional structures of the human factor XIa catalytic domain (XIcat) bound to a ligand were determined by x-ray diffraction crystallog. A series of amino acid substitution mutants that alter the ability of recombinant human factor XI to be glycosylated in the host and to improve crystallization are also provided. These structures are used to homol.
model the structure of other candidate inhibitors with XIcat. In addition, the methods described for the crystallization and structural determination of complexes of

XIcat with a ligand are used to exptl. determine the structure of other ligands bound to XIcat. This structural information is used to identify functional groups within a ligand that can be modified to increase the affinity and selectivity of the ligand for factor XIa or to identify functional groups within the ligand that can be modified to increase the bioavailability of the ligand without adversely affecting its affinity for factor XIa. In addition to providing compds. designed based on the structure of XIcat, the present invention includes a class of peptidomimetics and non-peptides that inhibit the activity of factor XIa, and thus useful for treating or preventing diseases for which inhibition of factor XIa is desirable.

IC ICM A61K

CC 7-5 (Enzymes)
Section cross-reference(s): 1, 63, 75

IT Protein sequences
(of human blood-coagulation factor XIa **mutants**; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 618-39-3D, Benzamidine, coagulation **factor XI catalytic domain** complexes **9013-55-2D**, Blood-coagulation **factor XI**, ligand complexes 37203-61-5D, Blood-coagulation factor XIa, ligand complexes 87928-05-0D, Ecotin, coagulation **factor XI catalytic domain** complexes
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

L77 ANSWER 11 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:878270 CAPLUS
DOCUMENT NUMBER: 141:360682
TITLE: Blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis
INVENTOR(S): Abdel-Meguid, Sherin S.; Babine, Robert E.; Deng, Hongfeng; Jin, Lei; Lin, Jian; Magee, Scott R.; Meyers, Harold V.; Pandey, Pramod; Rynkiewicz, Michael J.; Weaver, David T.
PATENT ASSIGNEE(S): Suntory Pharmaceutical Research Laboratories, LLC, USA
SOURCE: PCT Int. Appl., 251 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089297	A2	20041021	WO 2004-US10300	20040402

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,

SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005143317 A1 20050630 US 2004-817248 20040402
PRIORITY APPLN. INFO.: US 2003-459910P P 20030402
OTHER SOURCE(S): MARPAT 141:360682
ED Entered STN: 22 Oct 2004
AB The present invention provides compds. AX(R3)CH(R2)CONHCH(R1)[(C:O)]mR0 [R1 = alkyl-ω-NH2, (substituted)one- or two-ring heterocycle, etc.; R0,R2,R3 = (substituted)C1-6-alkyl, etc.; X = C, N; A = α-amino-substituted AA2; AA2 = peptide chain of 1-5 α-amino acids; m = 0, 1] which inhibit Factor XIa and methods of preventing or treating undesired thrombosis by administering a compound of the invention to a mammal. The invention also provides three-dimensional structures of Factor XIa and methods for designing or selecting addnl. Factor XIa inhibitors using these structures.
IC ICM A61K
CC 1-8 (Pharmacology)
Section cross-reference(s): 75
IT Heart, disease
(angina pectoris; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Anticoagulants
Atherosclerosis
Embolism
Human
Thrombosis
(blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Medical goods
(catheters, thrombosis resulting from; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Lung, disease
(embolism; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Blood
(**factor XI mutations** enhancing lifetime in; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Solubility
(**factor XI mutations** enhancing; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Dialysis
(hemodialysis, thrombosis resulting from; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Prosthetic materials and Prosthetics
(implants, thrombosis resulting from; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Heart, disease
(infarction; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Crystal structure
(of human **factor XI** complexed with inhibitors; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Embolism
(pulmonary; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)
IT Computer application

(rational drug design; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT Medical goods
(stents, thrombosis resulting from; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT Brain, disease
Brain, disease
(stroke; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT Inflammation
Vein, disease
(thrombophlebitis; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT Cardiopulmonary bypass
(thrombosis resulting from; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT 779359-46-5 779359-47-6 779359-48-7 779359-49-8 779359-50-1
779359-51-2 779359-52-3 779359-53-4 779359-54-5 779359-55-6
779359-56-7 779359-57-8 779359-58-9 779359-59-0 779359-60-3
779359-61-4 779359-62-5 779359-63-6
RL: PRP (Properties)
(amino acid sequence; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT **9013-55-2**, Blood-coagulation **factor XI**
37203-61-5, Blood-coagulation factor XIa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT 333716-21-5, GenBank AF356627 350008-08-1, GenBank AF395821
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT 70-11-1, 2-Bromo-1-phenylethanone 100-46-9, Benzylamine, reactions
4070-48-8 5292-43-3 5538-51-2, O-Acetylsalicyloyl chloride
6638-79-5, N,O-Dimethylhydroxylamine hydrochloride 52927-22-7,
6-Hydroxynaphthalene-2-carbonitrile 61008-98-8 68635-22-3 81560-03-4
132131-24-9, 2-Amino-5-iodobenzonitrile 167678-46-8 776304-99-5
776306-22-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT 141-90-2P, 2-Thiouracil 5751-20-2P 308276-66-6P 776305-00-1P
776305-01-2P 776305-04-5P 776305-05-6P 776305-06-7P 776305-07-8P
776305-09-0P 776305-10-3P 776305-11-4P 776305-12-5P 776305-13-6P
776305-14-7P 776305-15-8P 776305-17-0P 776305-18-1P 776305-19-2P
776305-20-5P 776305-21-6P 776305-23-8P 776305-24-9P 776305-25-0P
776305-26-1P 776305-27-2P 776305-28-3P 776305-29-4P 776305-30-7P
776305-31-8P 776305-32-9P 776305-33-0P 776305-34-1P 776305-35-2P
776305-36-3P 776305-75-0P 776305-76-1P 776305-99-8P 776306-00-4P
776306-01-5P 776306-08-2P 776306-09-3P 776306-12-8P 776306-13-9P
776306-23-1P 776306-24-2P 776306-86-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT 220298-06-6P 220298-55-5P 294865-55-7P 776305-37-4P 776305-38-5P
776305-39-6P 776305-40-9P 776305-41-0P 776305-42-1P 776305-43-2P
776305-44-3P 776305-45-4P 776305-46-5P 776305-47-6P 776305-48-7P
776305-50-1P 776305-52-3P 776305-53-4P 776305-54-5P 776305-55-6P

776305-56-7P 776305-57-8P 776305-58-9P 776305-59-0P 776305-60-3P
776305-61-4P 776305-62-5P 776305-63-6P 776305-64-7P 776305-65-8P
776305-66-9P 776305-67-0P 776305-68-1P 776305-69-2P 776305-70-5P
776305-71-6P 776305-73-8P 776305-74-9P 776305-77-2P 776305-78-3P
776305-80-7P 776305-81-8P 776305-82-9P 776305-84-1P 776305-85-2P
776305-86-3P 776305-87-4P 776305-88-5P 776305-89-6P 776305-90-9P
776305-91-0P 776305-92-1P 776305-93-2P 776305-94-3P 776305-95-4P
776305-96-5P 776305-98-7P 776306-02-6P 776306-03-7P 776306-04-8P
776306-05-9P 776306-06-0P 776306-07-1P 776306-14-0P 776306-15-1P
776306-16-2P 776306-17-3P 776306-18-4P 776306-19-5P 776306-20-8P
776306-21-9P 776306-25-3P 776306-26-4P 776306-27-5P 776306-28-6P
776306-30-0P 776306-31-1P 776306-32-2P 776306-33-3P 776306-34-4P
776306-35-5P 776306-36-6P 776306-37-7P 776306-38-8P 776306-39-9P
776306-40-2P 776306-41-3P 776306-42-4P 776306-43-5P 776306-44-6P
776306-45-7P 776306-46-8P 776306-85-5P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT 618-39-3D, Benzamidine, complex with **factor XI catalytic domain** 87928-05-0D, Ecotin, complex with **factor XI catalytic domain**
RL: PRP (Properties)
(crystal structure of; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

IT 779371-76-5
RL: PRP (Properties)
(unclaimed sequence; blood coagulation **factor XI** inhibitors and methods for treatment of thrombosis)

L77 ANSWER 12 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2004:492065 CAPLUS
DOCUMENT NUMBER: 141:188944
TITLE: Severe **factor XI** deficiency in a Lebanese family: identification of a novel missense **mutation** (Trp501Cys) in the **catalytic domain**
AUTHOR(S): de Moerloose, Philippe; Germanos-Haddad, Myrna; Boehlen, Francoise; Neerman-Arbez, Marguerite
CORPORATE SOURCE: Haemostasis Unit, Geneva University Hospital, Switz.
SOURCE: Blood Coagulation & Fibrinolysis (2004), 15(3), 269-272
CODEN: BLFIE7; ISSN: 0957-5235
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 18 Jun 2004
AB In this study, a Lebanese woman with severe factor XI deficiency as well as several unaffected family members were analyzed. The F11 gene was screened by polymerase chain reaction amplification of all 15 exons, including intron-exon junctions, followed by single-strand conformational anal. (SSCA). Variant SSCA profiles were obtained for exon 13 and sequencing of these products revealed a novel missense mutation (Trp501Cys) situated in the catalytic domain, in homozygosity in said Lebanese woman. Although in the absence of expression studies the authors cannot exclude that it is a rare polymorphism rather than mutation, several facts suggest that the Trp501Cys is indeed the mutation leading to factor XI deficiency.
CC 14-6 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

ST **factor XI** severe deficiency gene F11 missense **mutation** Lebanon; missense **mutation** F11 woman Lebanon **factor XI** severe deficiency

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(F11; identification of novel missense **mutation** (Trp501Cys) in **factor XI** gene F11 most likely responsible for severe **factor XI** deficiency in Lebanese woman)

IT Human groups
(Lebanese; identification of novel missense **mutation** (Trp501Cys) in **factor XI catalytic domain** most likely responsible for severe **factor XI** deficiency in Lebanese woman)

IT Blood coagulation
(disorder, **factor XI** deficiency; identification of novel missense **mutation** (Trp501Cys) in **factor XI catalytic domain** most likely responsible for severe **factor XI** deficiency in Lebanese woman)

IT Human
(identification of novel missense **mutation** (Trp501Cys) in **factor XI catalytic domain** most likely responsible for severe **factor XI** deficiency in Lebanese woman)

IT **Mutation**
(missense, Trp501→Cys; identification of novel missense **mutation** (Trp501Cys) in **factor XI catalytic domain** most likely responsible for severe **factor XI** deficiency in Lebanese woman)

IT **9013-55-2**, Blood-coagulation **factor XI**
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(deficiency of; identification of novel missense **mutation** (Trp501Cys) in **factor XI catalytic domain** most likely responsible for severe **factor XI** deficiency in Lebanese woman)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 13 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 2004:571317 CAPLUS
DOCUMENT NUMBER: 141:188951
TITLE: Dominant **factor XI** deficiency caused by **mutations** in the **factor XI catalytic domain**
AUTHOR(S): Kravtsov, Dmitri V.; Wu, Wenman; Meijers, Joost C. M.; Sun, Mao-Fu; Blinder, Morey A.; Dang, Thao P.; Wang, Hongli; Gailani, David
CORPORATE SOURCE: Departments of Pathology and Medicine, Vanderbilt University, Nashville, TN, USA
SOURCE: Blood (2004), 104(1), 128-134
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 18 Jul 2004
AB The bleeding diathesis associated with hereditary factor XI (fXI) deficiency is prevalent in Ashkenazi Jews, in whom the disorder appears to be an autosomal recessive condition. The homodimeric structure of fXI implies that the product of a single mutant allele could confer disease in a dominant manner through formation of heterodimers with wild-type

polypeptide. We studied 2 unrelated patients with fXI levels less than 20% of normal and family histories indicating dominant disease transmission. Both are heterozygous for single amino acid substitutions in the fXI catalytic domain (Gly400Val and Trp569Ser). Neither mutant is secreted by transfected fibroblasts. In cotransfection expts. with a wild-type fXI construct, constructs with mutations common in Ashkenazi Jews (Glu117Stop and Phe283Leu) and a variant with a severe defect in dimer formation (fXI-Gly350Glu) have little effect on wild-type fXI secretion. In contrast, cotransfection with fXI-Gly400Val or fXI-Trp569Ser reduces wild-type secretion about 50%, consistent with a dominant neg. effect. Immunopptn. of cell lysates confirmed that fXI-Gly400Val forms intracellular dimers. The data support a model in which nonsecretable mutant fXI polypeptides trap wild-type polypeptides within cells through heterodimer formation, resulting in lower plasma fXI levels than in heterozygotes for mutations that cause autosomal recessive fXI deficiency.

CC 14-6 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3, 7

ST fXI **catalytic domain mutation factor XI** deficiency diathesis

IT Blood coagulation
(disorder, hemorrhagic diathesis; dominant **factor XI** deficiency caused by **mutations** in **factor XI catalytic domain**)

IT Alleles
Enzyme functional sites
Genotypes
Human
Molecular association
Mutation
(dominant **factor XI** deficiency caused by **mutations** in **factor XI catalytic domain**)

IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(fXI; dominant **factor XI** deficiency caused by **mutations** in **factor XI catalytic domain**)

IT **Mutation**
(substitution; dominant **factor XI** deficiency caused by **mutations** in **factor XI catalytic domain**)

IT **9013-55-2**, Blood-coagulation **factor XI**
37203-61-5, Factor XIa
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(dominant **factor XI** deficiency caused by **mutations** in **factor XI catalytic domain**)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 14 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2001:13897 CAPLUS
DOCUMENT NUMBER: 134:351642
TITLE: A **factor XI** deficiency associated with a nonsense **mutation** (Trp501stop) in the **catalytic domain**
AUTHOR(S): Iijima, Kenji; Udagawa, Akihide; Kawasaki, Hironaka;

Murakami, Fumiyo; Shimomura, Tokio; Ikawa, Shiro
CORPORATE SOURCE: Division of Clinical Laboratory, Tottori University Hospital, Yonago, 683-8504, Japan
SOURCE: British Journal of Haematology (2000), 111(2), 556-558
CODEN: BJHEAL; ISSN: 0007-1048
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 08 Jan 2001
AB The authors identified a novel mutation in an asymptomatic 65-yr-old Japanese man with severe factor XI deficiency. Sequence anal. after polymerase chain reaction single-stranded conformation polymorphism (PCR-SSCP) anal. of his factor XI gene revealed a G→A transition in codon 501 of exon 13, resulting in a substitution of Trp501 (TGG) by a stop codon (TAG) in the catalytic domain. This mutation abolished a restriction site. The PCR product from normal subjects was digested with FokI and yielded two fragments, one of 223 bp and one of 47 bp. The PCR product from the patient gave a single 270-bp fragment, demonstrating possible homozygosity.
CC 14-6 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3
ST **factor XI** deficiency nonsense **mutation**
Trp501stop **catalytic domain**
IT Enzyme functional sites
(active; **factor XI** deficiency associated with nonsense **mutation** (Trp501stop) in **catalytic domain** in human)
IT Genetic element
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(exon, 13; **factor XI** deficiency associated with nonsense **mutation** (Trp501stop) in **catalytic domain** in human)
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(**factor XI** deficiency associated with nonsense **mutation** (Trp501stop) in **catalytic domain** in human)
IT **Mutation**
(nonsense; **factor XI** deficiency associated with nonsense **mutation** (Trp501stop) in **catalytic domain** in human)
IT **Mutation**
(transition; **factor XI** deficiency associated with nonsense **mutation** (Trp501stop) in **catalytic domain** in human)
IT **9013-55-2**, Blood-coagulation **factor XI**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(**factor XI** deficiency associated with nonsense **mutation** (Trp501stop) in **catalytic domain** in human)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 15 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:313407 CAPLUS
TITLE: Homozygosity for a Thr575Met missense **mutation** in the **catalytic domain** associated with **factor XI** deficiency
AUTHOR(S): Germanos-Haddad, Myrna; de Moerloose, Philippe; Boehlen, Francoise; Peyvandi, Flora; Neerman-Arbez, Marguerite
CORPORATE SOURCE: Hematology and Immunology Laboratory, Hotel-Dieu Hospital, Beirut, Lebanon
SOURCE: Haematologica (2005), 90(3), 418-419
CODEN: HAEMAX; ISSN: 0390-6078
PUBLISHER: Ferrata Storti Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 13 Apr 2005
AB In this study we investigated an asymptomatic 55-yr-old Lebanese woman with factor XI deficiency. The F11 gene was analyzed and a cross reacting material pos. (CRM+) variant, Thr575Met, was identified in homozygosity in the proband, and in heterozygosity in four of her siblings.
CC 14 (Mammalian Pathological Biochemistry)
ST missense **mutation** homozygosity **factor XI** deficiency
IT INDEXING IN PROGRESS
IT Human
Human groups
(F11 gene anal. revealed missense **mutation** in cross reacting material variant, Thr575Met with homozygosity in proband, and in heterozyosity in sibling of Lebanese women with **factor XI** deficiency)
IT Genotypes
(homozygosity; F11 gene anal. revealed missense **mutation** in cross reacting material variant, Thr575Met with homozygosity in proband, and in heterozyosity in sibling of Lebanese women with **factor XI** deficiency)
IT **Mutation**
(missense; F11 gene anal. revealed missense **mutation** Thr575Met in **catalytic domain** was identified in homozygosity in proband and in heterozyosity in sibling of Lebanese women with **factor XI** deficiency)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 16 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:129867 CAPLUS
DOCUMENT NUMBER: 142:259141
TITLE: Structural interpretation of 42 **mutations** causing **factor XI** deficiency using homology modeling
AUTHOR(S): O'Connell, N. M.; Saunders, R. E.; Lee, C. A.; Perry, D. J.; Perkins, S. J.
CORPORATE SOURCE: The Katharine Dormandy Haemophilia Center and Haemostasis Unit, The Royal Free and University College Medical School, London, UK
SOURCE: Journal of Thrombosis and Haemostasis (2005), 3(1), 127-138
CODEN: JTHOA5; ISSN: 1538-7933
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 15 Feb 2005

AB Factor (F)XI is important in the consolidation phase of blood coagulation. The structural effects of mutations causing FXI deficiency have not been well described due to the lack of a structure for FXI. To develop mol. models of the four apple (Ap) and serine protease (SP) domains in FXI in order to assess the structural effects of published FXI mutations in the light of their phenotypes. The Ap domains were modeled using the NMR structure of an adhesin from Eimeria tenella. The SP domain was modeled using the crystal structure of β-tryptase. The effect of 42 mutations causing FXI deficiency was analyzed using homol. models for the Ap and SP domains in FXI. Protein misfolding was implicated as the likely structural mechanism of disease in six of 14 mutations in the four Ap domains with Type I phenotypes. Likewise, misfolding was implicated in eight of 14 mutations in the SP domain with Type I phenotypes. Unlike other coagulation factor deficiencies, Type II phenotypes based on a catalytically dysfunctional FXI are uncommon. The structural models indicated that two known Type II mutations in the Ap domains could be correlated with functional defects in substrate or cofactor binding, and likewise four Type II mutations in the SP domain would disrupt the active site. New FXI disease-causing mutations can now be structurally characterized to complement phenotypic data, and expression studies can be designed to verify the mol. basis of each deficiency.

CC 14-6 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 7

ST **factor XI** deficiency **mutation** mol modeling

IT Enzyme functional sites
(active, serine proteinase domain; structural interpretation of 42 **mutations** causing **factor XI** deficiency using homol. modeling)

IT Protein motifs
(apple domain; structural interpretation of 42 **mutations** causing **factor XI** deficiency using homol. modeling)

IT Blood coagulation
(disorder; structural interpretation of 42 **mutations** causing **factor XI** deficiency using homol. modeling)

IT **Protein folding**
(misfolding; structural interpretation of 42 **mutations** causing **factor XI** deficiency using homol. modeling)

IT **Mutation**
(missense; structural interpretation of 42 **mutations** causing **factor XI** deficiency using homol. modeling)

IT Human
Molecular modeling
(structural interpretation of 42 **mutations** causing **factor XI** deficiency using homol. modeling)

IT **9013-55-2**, Blood-coagulation **factor XI**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structural interpretation of 42 **mutations** causing **factor XI** deficiency using homol. modeling)

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 17 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:355085 CAPLUS
DOCUMENT NUMBER: 140:369944
TITLE: Human tissue-specific housekeeping genes identified by expression profiling
INVENTOR(S): Aburatani, Hiroyuki; Yamamoto, Shogo
PATENT ASSIGNEE(S): NGK Insulators, Ltd., Japan
SOURCE: PCT Int. Appl., 372 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035785	A1	20040429	WO 2002-JP10753	20021016
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004229233	A1	20041118	US 2003-684422	20031015
PRIORITY APPLN. INFO.:			US 2002-418614P P	20021016
			WO 2002-JP10753 W	20021016

ED Entered STN: 30 Apr 2004

AB Housekeeping genes commonly expressed in 35 different human tissues, oligonucleotide probes and DNA microarrays containing them, are disclosed.

IC ICM C12N015-11
ICS C12Q001-68; G01N033-566

CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 13

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (CDH22 (**cadherin**-like 22); human tissue-specific housekeeping genes identified by expression profiling)

IT Cell adhesion **molecules**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (CEACAM7 (carcinoembryonic antigen-related cell adhesion mol. 7); human tissue-specific housekeeping genes identified by expression profiling)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Cbp/p300-interacting transactivator, with Glu/Asp-rich **carboxy** -**terminal** domain, 1, gene CITED1; human tissue-specific housekeeping genes identified by expression profiling)

IT **Proteins**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (DKFZP434D174 protein, gene DKFZP434D174; human tissue-specific housekeeping genes identified by expression profiling)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (JIP-2 (**c**-Jun **N-terminal** kinase-interacting protein-2); human tissue-specific housekeeping genes identified by expression profiling)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (highly **charged** protein, gene D13S106E; human tissue-specific housekeeping genes identified by expression profiling)

IT **Calcium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (voltage-gated, **CACNA2D2** (**voltage**-dependent, alpha 2/delta subunit 2); human tissue-specific housekeeping genes identified by expression profiling)

IT **9013-55-2**, Plasma thromboplastin antecedent
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(coagulation **factor XI** (plasma thromboplastin antecedent), gene F11; human tissue-specific housekeeping genes identified by expression profiling)
IT 9023-90-9, Methylmalonyl Coenzyme A **mutase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene MUT; human tissue-specific housekeeping genes identified by expression profiling)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 18 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:681889 CAPLUS
DOCUMENT NUMBER: 139:290301
TITLE: Compound heterozygosity for two novel **mutations** in a severe **factor XI** deficiency
AUTHOR(S): Tsukahara, Akiko; Yamada, Takayuki; Takagi, Akira; Murate, Takashi; Matsushita, Tadashi; Saito, Hidehiko; Kojima, Tetsuhito
CORPORATE SOURCE: Department of Medical Technology, Nagoya University School of Health Sciences, Nagoya, Japan
SOURCE: American Journal of Hematology (2003), 73(4), 279-284
CODEN: AJHEDD; ISSN: 0361-8609
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Sep 2003
AB We identified 2 novel mutations in an asymptomatic 25-yr-old Japanese patient with severe factor XI deficiency. Direct sequencing anal. of PCR products from his factor XI gene revealed a G to T transversion in exon 12, resulting in the nonsense mutation (Glu447Stop) and a G insertion in 5 consecutive guanine nucleotides (501Trp(TGG)-502Gly(GGG)) in exon 13 that is expected to lead to the substitution of the last 105 amino acids (503Tyr-607Val) with 32 abnormal amino acid residues (503Val 534Thr) followed by stop codon. We also demonstrated that 2 mutations are associated with the sep. alleles in this patient, indicating compound heterozygosity for these mutations. Both mutations lead to the disruption of the catalytic domain structure of the FXI mol. and thus are responsible for his deficiency of factor XI.
CC 14-6 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3, 6
ST gene FXI **mutation** heterozygosity **catalytic domain factor XI** deficiency
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(FXI; compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)
IT Human
Protein motifs
(compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)
IT Genotypes
(heterozygosity; compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)

IT **Mutation**
(insertion; compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)
IT **Mutation**
(nonsense; compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)
IT **Mutation**
(substitution; compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)
IT **Mutation**
(transversion; compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)
IT **9013-55-2**, Blood-coagulation **factor XI**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(deficiency; compound heterozygosity for **mutations** leading to FXI **catalytic domain** disruption in **factor XI** deficiency)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 19 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:795994 CAPLUS
DOCUMENT NUMBER: 132:31744
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Ltd., UK
SOURCE: PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
GB 1998-12099	A	19980606
GB 1998-13291	A	19980620
GB 1998-13611	A	19980624
GB 1998-13835	A	19980627
GB 1998-14110	A	19980701
GB 1998-14580	A	19980707
GB 1998-15438	A	19980716
GB 1998-15574	A	19980718
GB 1998-15576	A	19980718
GB 1998-16085	A	19980724

GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

ED Entered STN: 17 Dec 1999

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the number of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide critical clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

IC ICM C12Q001-68
ICS C07K016-18

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 13, 14

IT **5**-HT receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(5-HT1F, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Antigens**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD108, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Antigens**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD136, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **CD** antigens
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD72, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Proteins**, specific or class

RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CREB-binding, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Proteins**, specific or class
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(FABP (fatty acid-binding protein), core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Gene**, animal
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(FDGDY, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Transcription** factors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(HAND1 and HAND2, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Mutation**
(deletion, detection of; gene probes used for genetic profiling in healthcare screening and planning)

IT **Mutation**
(duplication, detection of; gene probes used for genetic profiling in healthcare screening and planning)

IT **Proteins, specific or class**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(mesoderm-specific transcript, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT 50-56-6, Oxytocin, biological studies 70-18-8, biological studies 113-79-1 1393-25-5, Secretin 9000-81-1 9000-83-3 9000-86-6 9000-90-2 9000-92-4, Amylase 9000-94-6, Antithrombin 9000-96-8, Arginase 9000-97-9 9001-03-0 9001-05-2, Catalase 9001-06-3, Chitinase 9001-08-5 9001-10-9, Pepsinogen A 9001-12-1, Collagenase 9001-15-4 9001-16-5 9001-18-7 9001-24-5, Blood-coagulation factor V 9001-25-6, Blood-coagulation factor VII 9001-27-8 9001-28-9, Blood-coagulation factor IX 9001-29-0, Blood-coagulation factor X 9001-30-3, Blood-coagulation factor XII 9001-36-9 9001-39-2 9001-40-5 9001-41-6 9001-42-7 9001-45-0 9001-47-2, Glutaminase 9001-48-3 9001-50-7 9001-51-8 9001-52-9 9001-54-1, Hyaluronidase 9001-58-5 9001-59-6 9001-63-2, Lysozyme 9001-64-3 9001-67-6, Neuraminidase 9001-69-8 9001-75-6, Pepsin A 9001-80-3 9001-81-4 9001-83-6 9001-84-7, Phospholipase A2 9001-86-9, Phospholipase C 9001-88-1 9001-91-6, Plasminogen 9001-97-2 9002-02-2 9002-03-3 9002-10-2 9002-12-4 9002-61-3 9002-62-4, Prolactin, biological studies 9002-64-6, Parathormone 9002-68-0, Follicle-stimulating hormone 9002-71-5, Thyrotropin 9002-76-0, Gastrin (hormone) 9003-99-0, Peroxidase 9004-02-8 9004-10-8, Insulin, biological studies 9007-43-6, Cytochrome c, biological studies 9011-97-6, Cholecystokinin 9012-25-3 9012-31-1 9012-39-9 9012-42-4 9012-47-9 9012-49-1 9012-52-6 9012-56-0, Amidase 9012-78-6 9012-90-2 9012-93-5 9012-96-8 9013-02-9 9013-08-5 9013-18-7 9013-38-1 **9013-55-2**, Blood-coagulation **factor XI** 9013-56-3, Blood-coagulation factor XIII 9013-66-5 9013-75-6 9014-08-8 9014-19-1 9014-24-8 9014-36-2 9014-42-0, Thrombopoietin 9014-48-6, Transketolase 9014-51-1 9014-55-5 9014-56-6 9014-74-8 9015-67-2 9015-71-8, Corticotropin-releasing factor 9015-81-0

9015-82-1 9015-83-2 9015-85-4 9015-94-5, Renin, biological studies
9016-11-9 9016-12-0 9016-17-5 9016-18-6 9023-26-1, Coenzyme
A-transferase 9023-56-7 9023-58-9 9023-62-5 9023-64-7 9023-69-2
9023-70-5 9023-78-3 9023-90-9 9023-93-2 9023-94-3 9023-99-8
9024-25-3 9024-52-6 9024-58-2 9024-70-8 9024-78-6, Kynureninase
9024-93-5, Dihydroorotase 9024-99-1 9025-06-3 9025-10-9 9025-15-4,
Biotinidase 9025-26-7, Cathepsin D 9025-32-5 9025-35-8 9025-42-7
9025-43-8 9025-52-9, Trehalase 9025-54-1, Adenosylhomocysteinase
9025-62-1 9025-90-5 9026-22-6 9026-23-7 9026-51-1 9026-59-9
9026-89-5 9026-93-1 9027-03-6 9027-13-8 9027-21-8 9027-27-4,
β-Ureidopropionase 9027-33-2 9027-34-3 9027-43-4 9027-44-5
9027-46-7 9027-65-0 9027-67-2 9027-80-9 9027-81-0 9027-88-7
9027-89-8 9027-96-7 9028-04-0 9028-06-2 9028-11-9 9028-16-4
9028-21-1 9028-31-3 9028-35-7 9028-38-0 9028-41-5 9028-86-8
9028-93-7 9028-95-9 9029-12-3 9029-38-3 9029-49-6 9029-60-1
9029-61-2 9029-72-5 9029-73-6 9029-75-8 9029-83-8 9029-84-9
9029-87-2 9029-97-4 9030-08-4 9030-21-1 9030-42-6 9030-50-6
9030-53-9 9030-66-4 9030-74-4, Dihydropyrimidinase 9030-83-5
9030-87-9 9031-02-1 9031-11-2 9031-14-5 9031-28-1 9031-36-1
9031-37-2, Ceruloplasmin 9031-54-3, Sphingomyelinase C 9031-61-2
9031-72-5 9031-82-7 9031-86-1, Aspartoacylase 9031-98-5,
Carboxypeptidase 9032-02-4 9032-22-8 9032-28-4 9032-29-5
9032-59-1, Fumarylacetoacetase 9032-62-6 9032-76-2 9032-88-6
9032-89-7 9034-39-3, Somatoliberin 9034-40-6, Luteinizing
hormone-releasing factor 9035-34-1, Cytochrome a 9035-39-6, Cytochrome
b5 9035-51-2, Cytochrome P 450, biological studies 9035-54-5
9035-58-9, Blood-coagulation factor III 9035-74-9, Phosphorylase
9035-75-0, Chymotrypsinogen 9035-81-8, Trypsin inhibitor 9036-20-8
9036-22-0 9036-23-1 9036-37-7 9036-43-5 9037-14-3 9037-21-2
9037-42-7
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL
(Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic
profiling in healthcare screening and planning)

L77 ANSWER 20 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:795993 CAPLUS
DOCUMENT NUMBER: 132:31743
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Limited, UK
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964626	A2	19991216	WO 1999-GB1779	19990604

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2330929	AA	19991216	CA 1999-2330929		19990604
AU 9941586	A1	19991230	AU 1999-41586		19990604
AU 766544	B2	20031016			
AU 9941587	A1	19991230	AU 1999-41587		19990604
GB 2339200	A1	20000119	GB 1999-12914		19990604
GB 2339200	B2	20010912			
EP 1084273	A1	20010321	EP 1999-925207		19990604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2003528564	T2	20030930	JP 2000-553616		19990604
US 2003198970	A1	20031023	US 2002-206568		20020729
PRIORITY APPLN. INFO.:			GB 1998-12098	A	19980606
			GB 1998-28289	A	19981223
			GB 1998-16086	A	19980724
			GB 1998-16921	A	19980805
			GB 1998-17097	A	19980807
			GB 1998-17200	A	19980808
			GB 1998-17632	A	19980814
			GB 1998-17943	A	19980819
			US 1999-325123	B1	19990603
			WO 1999-GB1779	W	19990604

ED Entered STN: 17 Dec 1999

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the number of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide critical clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

IC ICM C12Q001-68
ICS C07K016-18

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 13, 14

IT **Melatonin** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(1A and 1B, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Gene**, animal
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(BRCD1, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Antigens**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD117, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **CD** antigens

RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD27, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Antigens**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD76, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Gene**, animal
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(EFMR, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Receptors**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(ELF-1 (Eph ligand family-1), core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **G proteins** (guanine nucleotide-binding proteins)
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(GNAO1 and GNB3 and GNG5 and GNAQ, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Mutation**
(deletion, detection of; gene probes used for genetic profiling in healthcare screening and planning)

IT **Mutation**
(duplication, detection of; gene probes used for genetic profiling in healthcare screening and planning)

IT **Growth factors, animal**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**neurite** extension factors, 2, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT 50-56-6, Oxytocin, biological studies 70-18-8, biological studies 113-79-1 1393-25-5, Secretin 9000-81-1 9000-83-3 9000-86-6 9000-90-2 9000-92-4, Amylase 9000-94-6, Antithrombin 9000-96-8, Arginase 9000-97-9 9001-03-0 9001-05-2, Catalase 9001-06-3, Chitinase 9001-08-5 9001-10-9, Pepsinogen A 9001-12-1, Collagenase 9001-15-4 9001-16-5 9001-18-7 9001-24-5, Blood-coagulation factor V 9001-25-6, Blood-coagulation factor VII 9001-27-8 9001-28-9, Blood-coagulation factor IX 9001-29-0, Blood-coagulation factor X 9001-30-3, Blood-coagulation factor XII 9001-36-9 9001-39-2 9001-40-5 9001-41-6 9001-42-7 9001-45-0 9001-47-2, Glutaminase 9001-48-3 9001-50-7 9001-51-8 9001-52-9 9001-54-1, Hyaluronidase 9001-58-5 9001-59-6 9001-63-2, Lysozyme 9001-64-3 9001-67-6, Neuraminidase 9001-69-8 9001-75-6, Pepsin A 9001-80-3 9001-81-4 9001-83-6 9001-84-7, Phospholipase A2 9001-86-9, Phospholipase C 9001-88-1 9001-91-6, Plasminogen 9001-97-2 9002-02-2 9002-03-3 9002-10-2 9002-12-4 9002-61-3 9002-62-4, Prolactin, biological studies 9002-64-6, Parathormone 9002-68-0, Follicle-stimulating hormone 9002-71-5, Thyrotropin 9002-76-0, Gastrin (hormone) 9003-99-0, Peroxidase 9004-02-8 9004-10-8, Insulin, biological studies 9007-43-6, Cytochrome c, biological studies 9011-97-6, Cholecystokinin 9012-25-3 9012-31-1 9012-39-9 9012-42-4 9012-47-9 9012-49-1 9012-52-6 9012-56-0, Amidase 9012-78-6 9012-90-2 9012-93-5 9012-96-8 9013-02-9 9013-08-5 9013-18-7 9013-38-1

9013-55-2, Blood-coagulation **factor XI**
9013-56-3, Blood-coagulation factor XIII 9013-66-5 9013-75-6
9014-08-8 9014-19-1 9014-24-8 9014-36-2 9014-42-0, Thrombopoietin
9014-48-6, Transketolase 9014-51-1 9014-55-5 9014-56-6 9014-74-8
9015-67-2 9015-71-8, Corticotropin-releasing factor 9015-81-0
9015-82-1 9015-83-2 9015-85-4 9015-94-5, Renin, biological studies
9016-11-9 9016-12-0 9016-17-5 9016-18-6 9023-26-1, Coenzyme
A-transferase 9023-56-7 9023-58-9 9023-62-5 9023-64-7 9023-69-2
9023-70-5 9023-78-3 9023-90-9 9023-93-2 9023-94-3 9023-99-8
9024-25-3 9024-52-6 9024-58-2 9024-70-8 9024-78-6, Kynureninase
9024-93-5, Dihydroorotase 9024-99-1 9025-06-3 9025-10-9 9025-15-4,
Biotinidase 9025-26-7, Cathepsin D 9025-32-5 9025-35-8 9025-42-7
9025-43-8 9025-52-9, Trehalase 9025-54-1, Adenosylhomocysteinase
9025-62-1 9025-90-5 9026-00-0 9026-22-6 9026-23-7 9026-51-1
9026-59-9 9026-89-5 9026-93-1 9027-03-6 9027-13-8 9027-21-8
9027-27-4, β-Ureidopropionase 9027-33-2 9027-34-3 9027-43-4
9027-44-5 9027-46-7 9027-65-0 9027-67-2 9027-80-9 9027-81-0
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9028-86-8 9028-93-7 9028-95-9 9029-12-3 9029-38-3 9029-49-6
9029-60-1 9029-61-2 9029-72-5 9029-73-6 9029-75-8 9029-83-8
9029-84-9 9029-87-2 9029-97-4 9030-08-4 9030-21-1 9030-42-6
9030-50-6 9030-53-9 9030-66-4 9030-74-4, Dihydropyrimidinase
9030-83-5 9030-87-9 9031-02-1 9031-11-2 9031-14-5 9031-28-1
9031-36-1 9031-37-2, Ceruloplasmin 9031-54-3, Sphingomyelinase C
9031-61-2 9031-72-5 9031-82-7 9031-86-1, Aspartoacylase 9031-98-5,
Carboxypeptidase 9032-02-4 9032-22-8 9032-28-4 9032-29-5
9032-59-1, Fumarylacetoacetase 9032-62-6 9032-76-2 9032-88-6
9032-89-7 9034-39-3, Somatoliberin 9034-40-6, Luteinizing
hormone-releasing factor 9035-34-1, Cytochrome a 9035-39-6, Cytochrome
b5 9035-51-2, Cytochrome P 450, biological studies 9035-54-5
9035-58-9, Blood-coagulation factor III 9035-74-9, Phosphorylase
9035-75-0, Chymotrypsinogen 9035-81-8, Trypsin inhibitor 9036-20-8
9036-22-0 9036-23-1 9036-37-7 9036-43-5 9037-14-3 9037-21-2
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL
(Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic
profiling in healthcare screening and planning)

L77 ANSWER 21 OF 32 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 15

ACCESSION NUMBER: 92207444 EMBASE
DOCUMENT NUMBER: 1992207444
TITLE: Apple four in human blood coagulation factor XI mediates dimer formation.
AUTHOR: Meijers J.C.M.; Mulvihill E.R.; Davie E.W.; Chung D.W.
CORPORATE SOURCE: Department of Biochemistry, University of Washington,Seattle, WA 98195, United States
SOURCE: Biochemistry, (1992) Vol. 31, No. 19, pp. 4680-4684.
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 920802
Last Updated on STN: 920802

ABSTRACT: Human blood coagulation factor XI is a dimer composed of two identical subunits. Each subunit contains four apple domains as tandem repeats followed by a serine protease region. A disulfide bridge between Cys321 of each fourth apple domain links the subunits together. The role of Cys321 in the dimerization of factor XI was examined by mutagenesis followed by expression of its cDNA in baby hamster kidney cells. The **recombinant** proteins were then purified from the tissue culture medium and shown to have full biological activity. Normal **recombinant** factor XI was secreted as a dimer as determined by SDS-PAGE, while **recombinant** factor XI-Cys321Ser migrated as a monomer under these conditions. Gel filtration studies, however, revealed that each protein existed as a dimer under native conditions, indicating that the disulfide bond between Cys321 of each factor XI monomer was not necessary for dimer formation. The fourth apple domain (apple4) of factor XI was then introduced into tissue plasminogen activator (tPA) to investigate its role in the dimerization of other polypeptide chains. The fusion protein, containing apple4 (apple4-tPA), formed dimers as detected by SDS-PAGE and gel filtration. Furthermore, dimerization was specific to apple4, while apple3 had no effect on dimerization. These data further indicated that the apple4 domain of factor XI mediates dimerization of the two subunits and the interchain disulfide bond involving Cys321 was not essential for dimer formation.

CONTROLLED TERM: Medical Descriptors:
*dimerization
*protein domain
amino acid substitution
animal cell
article
disulfide bond
gene expression
hamster
human
kidney cell
mutagenesis
nonhuman
priority journal
Drug Descriptors:
*protein subunit
monomer
***blood clotting factor 11: EC, endogenous compound**
cysteine
plasminogen activator
recombinant protein
serine
serine proteinase inhibitor: EC, endogenous compound

CAS REGISTRY NO.: (blood clotting factor 11) 9013-55-2; (**cysteine**) 4371-52-2, 52-89-1, 52-90-4; (plasminogen activator) 9039-53-6; (serine) 56-45-1, 6898-95-9

L77 ANSWER 22 OF 32 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2005265579 EMBASE

TITLE: Characterization of blood coagulation factor XIT4751.

AUTHOR: McVey J.H.; Lal K.; Imanaka Y.; Kemball-Cook G.; Bolton-Maggs P.H.B.; Tuddenham E.G.D.

CORPORATE SOURCE: Dr. J.H. McVey, Department of Haemostasis and Thrombosis, MRC Clinical Sciences Centre, Imperial College London, Du Cane Road, London W12 0NN, United Kingdom. john.mcvey@csc.mrc.ac.uk

SOURCE: Thrombosis and Haemostasis, (2005) Vol. 93, No. 6, pp.

1082-1088.
Refs: 29
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
022 Human Genetics
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050630
Last Updated on STN: 20050630

ABSTRACT: PCR-SSCP and DNA sequence analysis of a factor XI (FXI) deficient patient (FXI:C 39 U/dL; FXI:Ag 27 U/dL) identified a C to T transition in exon 12 of the FXI gene (F11 c. 1521C>T) that predicts the substitution of Thr475 by Ile (FXI T4751) within the serine protease domain of FXI. This mutation destroys a consensus sequence for N-linked glycosylation, N473-Y-T475, known to be utilized in vivo. The FXIT4751 variant was generated by site-directed mutagenesis, together with other variants that could help explain the phenotype, and **recombinant** FXI variants were expressed in Chinese hamster ovary cells. FXI:Ag expression was analysed by Western blot analysis, ELISA and immunocytochemical staining. Wild-type FXI:Ag was secreted at high levels, however the mutant (FXIT4751) was secreted very poorly. Substitution of Thr475 by Ala, Pro, Lys or Arg (all of which abolish the glycosylation consensus sequence) also severely reduced the level of secreted FXI:Ag suggesting that glycosylation at Asn473 is required for folding or secretion. Concordant with this hypothesis the conservative substitution of Thr475 by Ser (which preserves the glycosylation consensus sequence) had no effect on FXI secretion. Thr/Ser475 is highly conserved in serine protease domains but the glycosylation site (Asn473) is not. Surprisingly, substitution of Asn473 by Ala (which removes the N-linked glycosylation site) had no effect on the levels of FXI:Ag secreted. In conclusion, although the FXI-T4751 mutation destroys an N-linked glycosylation consensus sequence, the cause of failure to secrete FXI is not the loss of a glycosylation site but rather a direct effect of the substitution of this highly conserved residue. .COPYRGT. 2005 Schattauer GmbH, Stuttgart.

CONTROLLED TERM: Medical Descriptors:
*blood clotting factor 11 deficiency
DNA sequence
exon
prediction
amino acid substitution
gene mutation
glycosylation
in vivo study
site directed mutagenesis
phenotype
gene expression
CHO cell
Western blotting
enzyme linked immunosorbent assay
immunocytochemistry
wild type
mutant
polymerase chain reaction
single strand conformation polymorphism
bleeding tendency
disease severity
genetic transfection

hematuria
in vitro study
human
nonhuman
male
case report
animal cell
adolescent
article
nucleotide sequence
priority journal
Drug Descriptors:
***blood clotting factor 11: EC, endogenous compound**
DNA: EC, endogenous compound
threonine: EC, endogenous compound
isoleucine: EC, endogenous compound
serine proteinase: EC, endogenous compound
alanine: EC, endogenous compound
proline: EC, endogenous compound
lysine: EC, endogenous compound
arginine: EC, endogenous compound
serine: EC, endogenous compound
asparagine: EC, endogenous compound

CAS REGISTRY NO.: (blood clotting factor 11) 9013-55-2; (DNA) 9007-49-2; (threonine) 36676-50-3, 72-19-5; (isoleucine) 7004-09-3, 73-32-5; (serine proteinase) 37259-58-8; (alanine) 56-41-7, 6898-94-8; (proline) 147-85-3, 7005-20-1; (lysine) 56-87-1, 6899-06-5, 70-54-2; (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (serine) 56-45-1, 6898-95-9; (asparagine) 70-47-3, 7006-34-0

GENE NUMBER: GENBANK M13142 referred number

L77 ANSWER 23 OF 32 EMBASE on STN

ACCESSION NUMBER: 1999028541 EMBASE

TITLE: Identification of a novel mutation in a non-Jewish factor XI deficient kindred.

AUTHOR: Alhaq A.; Mitchell M.; Sethi M.; Rahman S.; Flynn G.; Boulton P.; Caeno G.; Smith M.; Savidge G.

CORPORATE SOURCE: Dr. A. Alhaq, Haemophilia Centre, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom

SOURCE: British Journal of Haematology, (1999) Vol. 104, No. 1, pp. 44-49.
Refs: 27
ISSN: 0007-1048 CODEN: BJHEAL

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19990218
Last Updated on STN: 19990218

ABSTRACT: The role of factor XI (FXI) in blood coagulation has been clarified in recent years by descriptions of FXI-deficient patients who are prone to excessive bleeding after haemostatic challenge. We have studied a large kindred of an Italian FXI-deficient patient with a previously undescribed mutation. The propositus, a 68-year-old woman, presented with a cerebral thromboembolic event but had no history of bleeding (FXI activity 1.6 U/dl). A

sensitive ELISA failed to detect FXI antigen in the propositus. Sequence analysis of the entire FXI gene revealed a TGG to TGC transversion in codon 228 of exon 7 (FXI-W228C). This missense mutation results in a Trp to Cys substitution within the third apple domain of FXI. We conclude that this novel mutation occurred in a structurally conserved region and may therefore have interfered with either chain folding and secretion or stability of FXI and was responsible for the inherited abnormality seen in this kindred. It is unclear why this kindred does not exhibit a bleeding tendency but it may correlate with a FXI-like antigen and factor IX binding activity expressed on platelets.

CONTROLLED TERM: Medical Descriptors:
*blood clotting factor 11 deficiency: DI, diagnosis
*blood clotting factor 11 deficiency: ET, etiology
***missense mutation**
occlusive cerebrovascular disease: ET, etiology
enzyme linked immunosorbent assay
amino acid substitution
nucleic acid base substitution
codon
exon
protein folding
protein stability
Italy
human
female
case report
aged
article
priority journal
Drug Descriptors:
***blood clotting factor 11: EC, endogenous compound**
tryptophan: EC, endogenous compound
cysteine: EC, endogenous compound
blood clotting factor 9: EC, endogenous compound
CAS REGISTRY NO.: (blood clotting factor 11) 9013-55-2; (tryptophan) 6912-86-3, 73-22-3; (**cysteine**) 4371-52-2, 52-89-1, 52-90-4; (blood clotting factor 9) 9001-28-9

L77 ANSWER 24 OF 32 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 93196882 EMBASE
DOCUMENT NUMBER: 1993196882
TITLE: Molecular defect in factor IX Tokyo: Substitution of valine-182 by alanine at position P2' in the second cleavage site by factor XIa resulting in impaired activation.
AUTHOR: Maekawa H.; Sugo T.; Yamashita N.; Kamiya K.; Umeyama H.; Miura N.; Naka H.; Nishimura T.; Yoshioka A.; Matsuda M.
CORPORATE SOURCE: Institute of Hematology, Jichi Medical School,Tochigi, Japan
SOURCE: Biochemistry, (1993) Vol. 32, No. 24, pp. 6146-6151. ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 930808
Last Updated on STN: 930808

ABSTRACT: Utilizing polymerase chain reaction and directly sequencing the amplified exon 6 of the factor IX gene derived from a mild hemophilia Bm patient, we have identified a T to C mutation at nucleotide 20 525. This point mutation predicted a Val182 to Ala substitution in the abnormal factor IX molecule, designated as factor IX Tokyo. The patient manifested a low factor IX activity and a moderately prolonged ox-brain prothrombin time but a normal factor IX antigen level in plasma. Immunopurified factor IX derived from the patient was found to have a normal molecular weight but a reduced specific activity (23% of normal). Limited proteolysis by activated factor XI or by a snake venom-derived factor X-activating enzyme was considerably delayed, indicating the presence of structural alteration(s) most probably at or near the second enzyme-cleavage site. Once activated, however, factor IXa Tokyo was able to activate factor X normally and was inactivated by antithrombin III also in a normal fashion. The structural model of factor IXa and a docking model of factor IX and activated factor VII (factor VIIa) suggested that the Val182 to Ala substitution would not affect the local conformation of the ***catalytic*** **domain.** This mutation would rather loosen the fitness of the molecule into the substrate-binding pocket of factor VIIa due to a shorter side chain of the Ala substitution at the P2' position of the second cleavage site.

CONTROLLED TERM: Medical Descriptors:
***amino acid substitution**
*hemophilia b
adolescent
article
blood clotting
case report
chemical structure
clinical feature
gene amplification
gene mutation
human
male
nucleotide sequence
point mutation
polymerase chain reaction
priority journal
protein determination
protein purification
prothrombin time
Drug Descriptors:
*blood clotting factor 9: EC, endogenous compound
alanine
blood clotting factor 11: EC, endogenous compound
valine

CAS REGISTRY NO.: (blood clotting factor 9) 9001-28-9; (alanine) 56-41-7, 6898-94-8; (blood clotting factor 11) 9013-55-2; (valine) 7004-03-7, 72-18-4

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ACCESSION NUMBER: 93057870 EMBASE
DOCUMENT NUMBER: 1993057870
TITLE: Deletion mutagenesis of high molecular weight kininogen light chain. Identification of two anionic surface binding subdomains.
AUTHOR: Kunapuli S.P.; DeLa Cadena R.A.; Colman R.W.
CORPORATE SOURCE: Sol Sherry Thrombosis Research Ctr., Temple University School of Medicine,Philadelphia, PA 19140, United States

SOURCE: Journal of Biological Chemistry, (1993) Vol. 268, No. 4, pp. 2486-2492.
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 930321
Last Updated on STN: 930321

ABSTRACT: The light chain (LC) of cleaved high molecular weight kininogen (HK) binds to anionic surfaces as well as the zymogens prekallikrein and factor XI and thus accelerates activation of the kallikrein-kinin, fibrinolytic, and coagulation pathways. The binding sites on HK LC for factor XI (amino acid residues 574-631) and prekallikrein (residues 583-613) have been localized to domain 6. Domain 5 (residues 438-520) has been postulated to contain the anionic surface binding subdomain. In order to define this subdomain we have expressed HK LC (residues Lys438-Ser644) as a fusion protein with glutathione-S-transferase (GST) in Escherichia coli and generated various HK LC deletion mutants. The **recombinant** HK LC (rHK LC) and various HK LC fragments were purified as GST fusion proteins by glutathione-Sepharose affinity chromatography from bacterial cell extracts. The rHK LC and ***recombinant*** fragments His459-Ser644, Glu466-Ser644, Leu483- Ser644, His493-Ser644, Lys438-Asp492, Lys438-Ser531, and His493-Lys520 inhibited 125I-HKa binding to kaolin, a model anionic surface used in the contact system, in a concentration-dependent manner. Deletion mutant proteins lacking domain 5, Thr521-Ser644 and Ser583- Ser644, did not inhibit the radiolabeled HKa binding to kaolin. The rHK LC and **recombinant** fragments Lys438-Asp492, Lys438-Ser531, His493-Ser644, His493-Lys520, Thr521-Ser644, and Ser583- Ser644 were radiolabeled with 125I and were then tested for their ability to bind to kaolin in the presence of fibrinogen and albumin. Except for the Thr521-Ser644 and Ser583-Ser644 fragments, all other radiolabeled HK LC deletion mutant proteins and rHK LC bound to kaolin in a concentration-dependent manner. This binding to kaolin was specific since it was inhibited by the addition of excess unlabeled HKa. The rHK LC, His493- Ser644 and Δ493-520 HK LC have coagulant activity, while other deletion mutant proteins did not exhibit coagulant properties. We conclude that there are at least two anionic surface binding subdomains, one in the histidine-glycine-rich region (Lys438-Asp492) and the other in the histidine-glycine-lysine-rich region (His493-Lys520), in the domain 5 of HK LC. Either subdomain, in the presence of the zymogen binding domain 6, is sufficient to impart coagulant activity to HK LC, while the presence of both did not increase the coagulant activity of HK LC additively.

CONTROLLED TERM: Medical Descriptors:
***deletion mutant**
affinity chromatography
article
binding site
blood clotting
concentration response
enzyme activation
enzyme binding
fibrinolysis
gene expression
priority journal
Drug Descriptors:
***blood clotting factor 11**
*hybrid protein
*kinin

*kininogen
*prekallikrein
CAS REGISTRY NO.: (blood clotting factor 11) 9013-55-2; (prekallikrein) 9055-02-1

L77 ANSWER 26 OF 32 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 2000:30687006 BIOTECHNO
TITLE: The role of high molecular weight kininogen and prothrombin as cofactors in the binding of factor XI A3 domain to the platelet surface
AUTHOR: Ho D.H.; Badellino K.; Baglia F.A.; Su M.-F.; Zhao M.-M.; Gailani D.; Walsh P.N.
CORPORATE SOURCE: K. Badellino, Sol Sherry Thrombosis Res. Center, Temple University School of Medicine, 3400 N. Broad St., Philadelphia, PA 19140, United States.
E-mail: pnw@astro.ocis.temple.edu
SOURCE: Journal of Biological Chemistry, (18 AUG 2000), 275/33 (25139-25145), 32 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: We have reported that prothrombin (1 μM) is able to replace high molecular weight kininogen (45 nM) as a cofactor for the specific binding of factor XI to the platelet (Baglia, F. A., and Walsh, P. N. (1998) Biochemistry 37, 2271-2281). We have also determined that prothrombin fragment 2 binds to the Apple 1 domain of factor XI at or near the site where high molecular weight kininogen binds. A region of 31 amino acids derived from high molecular weight kininogen (HK31-mer) can also bind to factor XI (Tait, J. F., and Fujikawa, K. (1987) J. Biol. Chemical 262, 11651-11656). We therefore investigated the role of prothrombin fragment 2 and HK31-mer as cofactors in the binding of factor XI to activated platelets. Our experiments demonstrated that prothrombin fragment 2 (1μM) or the HK31-mer (8 μM) are able to replace high molecular weight kininogen (45 nM) or prothrombin (1μM) as cofactors for the binding of factor XI to the platelet. To localize the platelet binding site on **factor XI**, we used **mutant** full-length **recombinant factor XI** molecules in which the platelet binding site in the Apple 3 domain was altered by alanine scanning **mutagenesis.** The **recombinant factor XI** with alanine substitutions at positions Ser.sup.2.sup.4.sup.8, Arg.sup.2.sup.5.sup.0, Lys.sup.2.sup.5.sup.5, Leu.sup.2.sup.5.sup.7, Phe.sup.2.sup.6.sup.0, or Gln.sup.2.sup.6.sup.3 were defective in their ability to bind to activated platelets. Thus, the interaction of factor XI with platelets is mediated by the amino acid residues Ser.sup.2.sup.4.sup.8, Arg.sup.2.sup.5.sup.0, Lys.sup.2.sup.5.sup.5, Leu.sup.2.sup.5.sup.7, Phe.sup.2.sup.6.sup.0, and Gln.sup.2.sup.6.sup.3 within the Apple 3 domain.

Searched by Barb O'Bryen, STIC 2-2518

CONTROLLED TERM: *protein domain; *protein binding; *thrombocyte membrane; *high molecular weight kininogen; *prothrombin; *blood clotting factor 11a; *amino acid; binding site; thrombocyte activation; amino acid substitution; amino acid analysis; protein localization; human; human cell; article; priority journal; serine; arginine; lysine; leucine; phenylalanine; glutamine

CAS REGISTRY NUMBER: (high molecular weight kininogen) 97792-85-3; (prothrombin) 9001-26-7; (amino acid) 65072-01-7; (serine) 56-45-1, 6898-95-9; (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (lysine) 56-87-1, 6899-06-5, 70-54-2; (leucine) 61-90-5, 7005-03-0; (phenylalanine) 3617-44-5, 63-91-2; (glutamine) 56-85-9, 6899-04-3

L77 ANSWER 27 OF 32 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 2000:30056465 BIOTECHNO

TITLE: Factor XI binding to activated platelets is mediated by residues R.sup.2.sup.5.sup.0, K.sup.2.sup.5.sup.5, F.sup.2.sup.6.sup.0, and Q.sup.2.sup.6.sup.3 within the apple 3 domain

AUTHOR: Ho D.H.; Baglia F.A.; Walsh P.N.

CORPORATE SOURCE: P.N. Walsh, Sol Sherry Thrombosis Res. Center, Temple University School of Medicine, 3400 N. Broad St., Philadelphia, PA 19140, United States.
E-mail: pnw@astro.ocis.temple.edu

SOURCE: Biochemistry, (18 JAN 2000), 39/2 (316-323), 32 reference(s)
CODEN: BICHAW ISSN: 0006-2960

DOCUMENT TYPE: Journal; Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: To localize the platelet binding site on factor XI, rationally designed, conformationally constrained synthetic peptides were used to compete with [.sup.1.sup.2.sup.5I]factor XI binding to activated platelets. The major platelet binding energy resided within the sequence of amino acids T.sup.2.sup.4.sup.9-F.sup.2.sup.6.sup.0. Homology scanning, using prekallikrein amino acid substitutions within the synthetic peptide T.sup.2.sup.4.sup.9-F.sup.2.sup.6.sup.0, identified a major role for R.sup.2.sup.5.sup.0 in platelet binding. Inhibition of [.sup.1.sup.2.sup.5I]factor XI binding to activated platelets by the **recombinant** Apple 3 domain of factor XI and inhibition by unlabeled factor XI were identical, whereas the **recombinant** Apple 3 domain of prekallikrein had little effect. A 'gain-of-function' chimera in which the **C-terminal amino** acid sequence of the Apple 3 domain of prekallikrein was replaced with that of factor XI was as effective as the **recombinant** Apple 3 domain of factor XI and unlabeled factor XI in inhibiting [.sup.1.sup.2.sup.5I]**factor XI** binding to activated platelets. Alanine scanning **mutagenic** analysis of the **recombinant**

Searched by Barb O'Bryen, STIC 2-2518

Apple 3 domain of **factor XI**
indicated that amino acids R.sup.2.sup.5.sup.0, K.sup.2.sup.5.sup.5, F.sup.2.sup.6.sup.0, and Q.sup.2.sup.6.sup.3 (but not K.sup.2.sup.5.sup.2 or K.sup.2.sup.5.sup.3) are important for platelet binding. Thus, the binding energy mediating the interaction of factor XI with platelets is contained within the **C-terminal**
amino acid sequence of the Apple 3 domain (T.sup.2.sup.4.sup.9-V.sup.2.sup.7.sup.1) and is mediated in part by amino acid residues R.sup.2.sup.5.sup.0, K.sup.2.sup.5.sup.5, F.sup.2.sup.6.sup.0, and Q.sup.2.sup.6.sup.3.

CONTROLLED TERM: *blood clotting factor 11; *prekallikrein; *amino acid; *thrombocyte activation; *protein binding; amino acid sequence; carboxy terminal sequence; protein domain; chimera; amino acid substitution; enthalpy; article; priority journal

CAS REGISTRY NUMBER: (blood clotting factor 11) 9013-55-2; (prekallikrein) 9055-02-1; (amino acid) 65072-01-7

L77 ANSWER 28 OF 32 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 1997:27211727 BIOTECHNO

TITLE: A murine model of factor XI deficiency

AUTHOR: Gailani D.; Lasky N.M.; Broze G.J. Jr.

CORPORATE SOURCE: G.J. Broze Jr., Division of Hematology, Jewish Hospital, Washington Univ. School of Medicine, 216 S. Kingshighway Boulevard, St. Louis, MO 63110, United States.

SOURCE: Blood Coagulation and Fibrinolysis, (1997), 8/2 (134-144), 35 reference(s)
CODEN: BLFIE7 ISSN: 0957-5235

DOCUMENT TYPE: Journal; Article

COUNTRY: United Kingdom

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: To facilitate investigations into the physiologic and pathologic roles of factor XI, we have developed a murine model of severe factor XI deficiency using the technique of homologous **recombination** in embryonic stem cells.The factor XI gene was disrupted by introducing a neomycin phosphotransferase gene into the fifth exon. The activated partial thromboplastin times of homozygous null mice were prolonged (158->200 s) compared with wild type (25-34 s) and heterozygous null (40-61 s) litter mates. Factor XI activity was absent from the plasma of mice homozygous for the null **mutation** and **factor XI**
mRNA was undetectable by Northern blot and reverse transcription/PCR in the livers of homozygous null animals. The genotypes of progeny from matings of mice heterozygous for the factor XI null allele followed the expected Mendelian ratio (1:2:1, wild type 26%, heterozygote null 54%, homozygous null 20%), indicating that severe factor XI deficiency did not result in increased intrauterine death. Results of a tail transection bleeding time assay were similar for wild type and homozygous null animals with, at most, a tendency for slightly prolonged bleeding in the

homozygous null animals. The factor XI deficient mice are a unique tool for evaluating the role of factor XI in normal hemostasis and pathologic coagulation.

CONTROLLED TERM: *blood clotting factor 11 deficiency; animal cell; animal experiment; animal model; article; gene targeting; mouse; nonhuman; priority journal

L77 ANSWER 29 OF 32 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 1994:25015130 BIOTECHNO

TITLE: Binding of high-molecular-mass kininogen to the Apple 1 domain of factor XI is mediated in part by Val.sup.6.sup.4 and Ile.sup.7.sup.7

AUTHOR: Seaman F.S.; Baglia F.A.; Gurr J.A.; Jameson B.A.; Walsh P.N.

CORPORATE SOURCE: Sol Sherry Thrombosis Research Ctr, Temple University School of Medicine, 3400 North Broad Street,Philadelphia, PA 19140, United States.

SOURCE: Biochemical Journal, (1994), 304/3 (715-721)
CODEN: BIJOAK ISSN: 0264-6021

DOCUMENT TYPE: Journal; Article

COUNTRY: United Kingdom

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: We have previously demonstrated the presence of a binding site for high-molecular-mass kininogen (HK), spanning residues Val.sup.5.sup.9-Lys.sup.8.sup.3, in the first Apple (A1) domain in the heavy-chain region of factor XI. We have now prepared conformationally constrained synthetic peptides and **recombinant** A1 domain (rA1) constructs to identify the specific amino acid residues that constitute the HK-binding site. Expression of the A1 domain (Glu.sup.1-Ser.sup.9.sup.0) was achieved in a bacterial expression system following PCR amplification of the A1 domain from factor XI cDNA and ligation into an expression plasmid. The rA1 inhibited factor XI binding to HK ¢K(i) .sim. (2-3) x 10.sup.-.sup.7 M! in a manner indistinguishable from purified factor XI, indicating that all the information necessary for binding HK is contained within the A1 domain. To identify specific amino acid residues involved in binding HK, conformationally constrained peptides were synthesized containing conservative amino acid substitutions at residues suspected to contain side chains involved in binding, including Val.sup.6.sup.4 → Ala, Glu.sup.6.sup.6 → Ala, Arg.sup.7.sup.3 → Ala and Ile.sup.7.sup.7 → Ala. Because normal results were obtained with all peptides with the exception of Val.sup.6.sup.4 → Ala and Ile.sup.7.sup.7 → Ala, which failed to compete normally with **factor XI** for binding to HK, we prepared two **mutant** rA1 domains (Val.sup.6.sup.4 → Ala and Ile.sup.7.sup.7 → Ala) by PCR-based site-directed **mutagenesis**, both of which exhibited diminished capacity to inhibit **factor XI** binding to HK. Competition studies with prekallikrein (PK) and a PK-dependent synthetic

peptide suggested that PK and factor XI have a common surface in the A1 domain for binding HK of which Val.sup.6.sup.4 is a part. We conclude that the binding of factor XI to HK is mediated at least in part by Val.sup.6.sup.4 and Ile.sup.7.sup.7 in the A1 domain of factor XI.

CONTROLLED TERM: *blood clotting factor 11; *high molecular weight kininogen; *protein domain; isoleucine; prekallikrein; valine; amino acid substitution; article; polymerase chain reaction; priority journal; protein protein interaction

CAS REGISTRY NUMBER: (blood clotting factor 11) 9013-55-2; (high molecular weight kininogen) 97792-85-3; (isoleucine) 7004-09-3, 73-32-5; (prekallikrein) 9055-02-1; (valine) 7004-03-7, 72-18-4

L77 ANSWER 30 OF 32 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN

ACCESSION NUMBER: 1994:24234486 BIOTECHNO

TITLE: Molecular genetics aspects of factor XI deficiency and Glanzmann thrombasthenia

AUTHOR: Seligsohn U.; Peretz H.

CORPORATE SOURCE: Chemical Pathology Laboratory, Tel Aviv Medical Center,Tel Aviv, Israel.

SOURCE: Haemostasis, (1994), 24/2 (81-85)
CODEN: HMTSB7 ISSN: 0301-0147

DOCUMENT TYPE: Journal; Conference Article

COUNTRY: Switzerland

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Factor XI deficiency and Glanzmann thrombasthenia are among the hereditary disorders frequently encountered in Israel. Factor XI deficiency is particularly frequent in Ashkenazi (European) Jews with 1:190 individuals affected by the severe deficiency and 8.1% of the population being heterozygotes. So far 4 **mutations** causing **factor XI** deficiency have been identified of which the type II (a non-sense mutation) and type III (a missense mutation) are predominant and type I and IV observed only in 5 families. Recently, the type II mutation was observed in Iraqui-Jews as well with 3.7% of 400 unrelated subjects being heterozygotes and with the type III mutation completely absent. Since Iraqui-Jews represent the original gene pool of Jews who lived in Babylon 2500 years ago we hypothesize that the type II mutation is ancient and that the type III mutation occured more recently, after the divergence of the original Babylonian Jews into Ashkenazi, Sephardic (Spanish) and Middle Eastern Jews. Preliminary data on factor XI intragenic polymorphic markers indeed indicate that type II and type III mutations reside on chromosomes each characterized by a different specific haplotype. Fifty living patients with type I Glanzmann thrombasthenia (28 families) have been observed in Israel. Most of them are Iraqui-Jewish and the rest are Arabs (5 families) and one Iranian Jewish. All Iraqui-Jewish patients have an IIbp deletion within exon 12 of the glycoprotein (GP) IIIa resulting in a shift of the reading frame that leads to premature termination of the GPIIIa synthesis. In 3 of the Arab

families a 13bp deletion was found in exon 4 of the GPIIb gene causing forced alternative splicing with 6 amino acids missing at the **N-terminal** region of GPIIb. For the detection of both mutations simple PCR methods were devised enabling carrier detection and prenatal diagnosis by CVS.

CONTROLLED TERM: *glanzmann disease; *hemophilia b; *molecular genetics; amino terminal sequence; chromosome polymorphism; conference paper; counseling; gene pool; genetic disorder; genetic heterogeneity; heterozygosity; human; nonsense mutation; prenatal diagnosis; priority journal

L77 ANSWER 31 OF 32 Elsevier BIOBASE COPYRIGHT 2005 Elsevier Science B.V.
on STN DUPLICATE

ACCESSION NUMBER: 2005057174 ESBIOBASE

TITLE: Crystal structures of the FXIa catalytic domain in complex with ecotin **mutants** reveal substrate-like interactions

AUTHOR: Jin L.; Pandey P.; Babine R.E.; Gorga J.C.; Seidl K.J.; Gelfand E.; Weaver D.T.; Abdel-Meguid S.S.; Strickler J.E.

CORPORATE SOURCE: L. Jin, Daiichi Asubio Med. Res. Labs. LLC, Cambridge, MA 02139, United States.
E-mail: lei.jin@daiamed.com

SOURCE: Journal of Biological Chemistry, (11 FEB 2005), 280/6 (4704-4712), 49 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258

DOCUMENT TYPE: Journal; Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Thrombosis can lead to life-threatening conditions such as acute myocardial infarction, pulmonary embolism, and stroke. Although commonly used anti-coagulant drugs, such as low molecular weight heparin and warfarin, are effective, they carry a significant risk of inducing severe bleeding complications, and there is a need for safer drugs. Activated **Factor XI** (FXIa) is a key enzyme in the amplification phase of the coagulation cascade. Anti-human FXI antibody significantly reduces thrombus growth in a baboon thrombosis model without bleeding problems (Gruber, A., and Hanson, S. R. (2003) Blood 102, 953-955). Therefore, FXIa is a potential target for anti-thrombosis therapy. To determine the structure of FXIa, we derived a recombinant catalytic domain of FXI, consisting of residues 370-607 (rhFXI.sub.3.sub.7.sub.0.sub.-.sub.6.sub.0.sub.7). Here we report the first crystal structure of rhFXI.sub.3.sub.7.sub.0.sub.-.sub.6.sub.0.sub.7 in complex with a substitution **mutant** of ecotin, a panserine protease protein inhibitor secreted by Escherichia coli, to 2.2 Å resolution. The presence of ecotin not only assisted in the **crystallization** of the enzyme but also revealed unique structural features in the active site of FXIa. Subsequently, the sequence from P5 to P2' in

ecotin was **mutated** to the FXIa substrate sequence, and the structures of the rhFXI.sub.3.sub.7.sub.0.sub.-.sub.6.sub.0.sub.7-ecotin **mutant** complexes were determined. These structures provide us with an understanding of substrate binding interactions of FXIa, the structural information essential for the structure-based design of FXIa-selective inhibitors.

CLASSIFICATION CODE: 82.2.3 PROTEIN BIOCHEMISTRY: STRUCTURAL STUDIES: Protein **Crystallization** and Crystal Structures

L77 ANSWER 32 OF 32 on STN Elsevier BIOBASE COPYRIGHT 2005 Elsevier Science B.V.

ACCESSION NUMBER: 2005032233 ESBIOBASE

TITLE: Mapping and functional characterization of the TAF11 interaction with TFIIA

AUTHOR: Robinson M.M.; Yatherajam G.; Ranallo R.T.; Bric A.; Paule M.R.; Stargell L.A.

CORPORATE SOURCE: L.A. Stargell, Dept. of Biochem. and Molec. Biology, Colorado State University, Fort Collins, CO 80523-1870, United States.
E-mail: Laurie.Stargell@ColoState.edu

SOURCE: Molecular and Cellular Biology, (2005), 25/3 (945-957), 61 reference(s)
CODEN: MCEBD4 ISSN: 0270-7306

DOCUMENT TYPE: Journal; Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: TFIIA interacts with TFIID via association with TATA binding protein (TBP) and TBP-associated **factor 11** (TAF11). We previously identified a **mutation** in the small subunit of TFIIA (toa2-I27K) that is defective for interaction with TAF11. To further explore the functional link between TFIIA and TAF11, the toa2-I27K allele was utilized in a genetic screen to isolate compensatory mutants in TAF11. Analysis of these compensatory mutants revealed that the interaction between TAF11 and TFIIA involves two distinct regions of TAF11: the highly conserved histone **fold** domain and the **N-terminal** region. Cells expressing a TAF11 allele defective for interaction with TFIIA exhibit conditional growth phenotypes and defects in transcription. Moreover, TAF11 imparts changes to both TFIIA-DNA and TBP-DNA contacts in the context of promoter DNA. These alterations appear to enhance the formation and stabilization of the TFIIA-TBP-DNA complex. Taken together, these studies provide essential information regarding the molecular organization of the TAF11-TFIIA interaction and define a mechanistic role for this association in the regulation of gene expression in vivo.

CLASSIFICATION CODE: 84.1.9.3 GENETICS AND MOLECULAR BIOLOGY: MOLECULAR GENETICS: Gene Expression in Eukaryotes: Transcriptional regulation

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     FILE 'CAPLUS' ENTERED AT 14:07:36 ON 26 JUL 2005
               SET LINE 250
               SET DETAIL OFF
               E US2003-817248/AP,PRN 25
               SET LINE LOGIN
               SET DETAIL LOGIN
L1           34 SEA ABB=ON  BABINE R?/AU
L2         1633 SEA ABB=ON  DENG H?/AU
L3            4 SEA ABB=ON  L1 AND L2
               D SCAN TI
               D SCAN
L4          698 SEA ABB=ON  FACTOR XI/OBI
L5         1659 SEA ABB=ON  CATALYTIC?/OBI(2A)DOMAIN#/OBI
L6       269242 SEA ABB=ON  CRYSTALLI?/OBI
L7       220829 SEA ABB=ON  CHARGE#/OBI
L8        12612 SEA ABB=ON  SULFHYDRYL/OBI
L9        53481 SEA ABB=ON  (N/OBI OR NH2/OBI OR AMINO/OBI OR COOH/OBI OR
               CARBOXY/OBI OR C/OBI)(2A)(TERMIN?/OBI OR END/OBI)
               E PROTEIN FOLDING/CT
               E E3+ALL
L10       13133 SEA ABB=ON  PROTEIN FOLDING/CT
L11           7 SEA ABB=ON  L4 AND L5
L12           5 SEA ABB=ON  L4 AND L6
L13           5 SEA ABB=ON  L4 AND L7
L14           0 SEA ABB=ON  L4 AND L8
L15          12 SEA ABB=ON  L4 AND L9
L16           1 SEA ABB=ON  L4 AND L10
L17      263445 SEA ABB=ON  MUTA?/OBI
L18          11 SEA ABB=ON  L4 AND L17 AND (L5 OR L6 OR L7 OR L8 OR L9 OR L10)


     FILE 'REGISTRY' ENTERED AT 14:14:27 ON 26 JUL 2005
               E BLOOD COAGULATION FACTOR/CN
L19            1 SEA ABB=ON  9013-55-2
               D SCAN

     FILE 'REGISTRY' ENTERED AT 14:15:37 ON 26 JUL 2005
               D IDE

     FILE 'CAPLUS' ENTERED AT 14:16:19 ON 26 JUL 2005
L20          785 SEA ABB=ON  L19
L21           11 SEA ABB=ON  (L4 OR L20) AND L17 AND (L5 OR L6 OR L7 OR L8 OR
               L9 OR L10)

     FILE 'MEDLINE' ENTERED AT 14:16:51 ON 26 JUL 2005
               E BLOOD COAG/CT
               E BLOOD COAGULATION FACTOR/CT
               E E7+ALL
               E E2+ALL
               E E12+ALL
L22          776 SEA ABB=ON  FACTOR XI/CT
L23        10335 SEA ABB=ON  CATALYTIC DOMAIN#
L24        66484 SEA ABB=ON  CRYSTALLI?
L25       291959 SEA ABB=ON  RECOMB?
L26        29513 SEA ABB=ON  SULFHYDRYL OR SULPHYDRYL
L27        62211 SEA ABB=ON  CYSTEINE
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Searched by Barb O'Bryen, STIC 2-2518

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L28       79025 SEA ABB=ON  CHARGE#
L29      150646 SEA ABB=ON  (N OR NH2 OR AMINO OR COOH OR CARBOXY OR C)(2A)(TER
                MIN? OR END)
                E PROTEIN FOLDING/CT
                E E3+ALL
L30       17497 SEA ABB=ON  PROTEIN FOLDING/CT
                D TRIAL L29 1-20
                D TRIAL L29 150000-150005
                E MUTA/CT
                E MUTATION/CT
                E E3+ALL
L31      349176 SEA ABB=ON  MUTATION+NT/CT
                E MUTANT/CT
                E MUTANTS/CT
L32          12 SEA ABB=ON  L22 AND L31 AND (L23 OR L24 OR L25 OR L26 OR L27
                OR L28 OR L29 OR L30)
                D TRIAL 1-5
L33          75 SEA ABB=ON  L22(L)GE/CT
L34           9 SEA ABB=ON  L33 AND L31 AND (L23 OR L24 OR L25 OR L26 OR L27
                OR L28 OR L29 OR L30)

     FILE 'EMBASE' ENTERED AT 14:23:14 ON 26 JUL 2005
                E FACTOR XI/CT
                E E3+ALL
L35         952 SEA ABB=ON  BLOOD CLOTTING FACTOR 11/CT
                E MUTATION/CT
                E E3+ALL
L36      283536 SEA ABB=ON  MUTATION+NT/CT
L37        5487 SEA ABB=ON  CATALYTIC DOMAIN#
L38       34732 SEA ABB=ON  CRYSTALLI?
L39      195282 SEA ABB=ON  RECOMB?
L40       10337 SEA ABB=ON  SULFHYDRYL OR SULPHYDRYL
L41       47196 SEA ABB=ON  CYSTEINE
L42       68461 SEA ABB=ON  CHARGE#
                E N-TERMIN/CT
                E N TERMIN/CT
                E N TERMINUS/CT
L43      142113 SEA ABB=ON  (N OR NH2 OR AMINO OR COOH OR CARBOXY OR C)(2A)(TER
                MIN? OR END)
                E PROTEIN FOLDING/CT
                E E3+ALL
L44       23189 SEA ABB=ON  PROTEIN FOLDING/CT
L45          25 SEA ABB=ON  L35 AND L36 AND (L37 OR L38 OR L39 OR L40 OR L41
                OR L42 OR L43 OR L44)
L46           5 SEA ABB=ON  L35/MAJ AND L36/MAJ AND (L37 OR L38 OR L39 OR L40
                OR L41 OR L42 OR L43 OR L44)
                D TRIAL L45 1-5
L47       30083 SEA ABB=ON  AMINO ACID SUBSTITUTION/CT
L48       55419 SEA ABB=ON  PROTEIN STRUCTURE/CT
L49           8 SEA ABB=ON  L35 AND L36 AND L47 AND ((L37 OR L38 OR L39 OR L40
                OR L41 OR L42 OR L43 OR L44) OR L48)

     FILE 'STNGUIDE' ENTERED AT 14:28:55 ON 26 JUL 2005

     FILE 'PASCAL, BIOTECHNO, ESBIOBASE, BIOSIS, CONFSCI, BIOTECHDS, DISSABS,
     WPIDS' ENTERED AT 14:31:41 ON 26 JUL 2005
L50        2615 SEA ABB=ON  FACTOR(W)(XI OR 11)
L51     1347005 SEA ABB=ON  MUTA?
L52       20342 SEA ABB=ON  CATALYTIC?(2A) DOMAIN#
L53      452523 SEA ABB=ON  CRYSTALLI?
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L54      762450 SEA ABB=ON  RECOMB?
L55       29423 SEA ABB=ON  SULFHYDRYL OR SULPHYDRYL
L56      138934 SEA ABB=ON  CYSTEINE
L57      831908 SEA ABB=ON  CHARGE#
L58      440145 SEA ABB=ON  (N OR NH2 OR AMINO OR COOH OR CARBOXY OR C)(2A)(TER
                MIN? OR END)
L59      870620 SEA ABB=ON  FOLD###
L60         160 SEA ABB=ON  L50 AND L51 AND (L52 OR L53 OR L54 OR L55 OR L56
                OR L57 OR L58 OR L59)
L61         349 SEA ABB=ON  L50 AND L51
L62          28 SEA ABB=ON  L61 AND L52
L63           4 SEA ABB=ON  L61 AND L53
L64         100 SEA ABB=ON  L61 AND L54
L65           2 SEA ABB=ON  L61 AND L55
L66          10 SEA ABB=ON  L61 AND L56
L67          14 SEA ABB=ON  L61 AND L57
L68          34 SEA ABB=ON  L61 AND L58
L69          37 SEA ABB=ON  L61 AND L59
L70           9 DUP REM L66 (1 DUPLICATE REMOVED)
                     ANSWERS '1-4' FROM FILE BIOTECHNO
                     ANSWERS '5-6' FROM FILE BIOSIS
                     ANSWER '7' FROM FILE DISSABS
                     ANSWERS '8-9' FROM FILE WPIDS
L71          58 SEA ABB=ON  L50(8A) L51 AND (L52 OR L54 OR (L56 OR L57 OR L58
                OR L59))
L72          30 SEA ABB=ON  L50(8A) L51 (S) (L52 OR L54 OR (L56 OR L57 OR L58
                OR L59))
L73          14 DUP REM L72 (16 DUPLICATES REMOVED)
                     ANSWERS '1-5' FROM FILE PASCAL
                     ANSWERS '6-10' FROM FILE BIOTECHNO
                     ANSWER '11' FROM FILE ESBIOBASE
                     ANSWER '12' FROM FILE BIOSIS
                     ANSWERS '13-14' FROM FILE WPIDS
L74          27 DUP REM L71 (31 DUPLICATES REMOVED)
                     ANSWERS '1-8' FROM FILE PASCAL
                     ANSWERS '9-14' FROM FILE BIOTECHNO
                     ANSWERS '15-16' FROM FILE ESBIOBASE
                     ANSWERS '17-24' FROM FILE BIOSIS
                     ANSWER '25' FROM FILE BIOTECHDS
                     ANSWERS '26-27' FROM FILE WPIDS

     FILE 'STNGUIDE' ENTERED AT 14:37:15 ON 26 JUL 2005

     FILE 'CAPLUS' ENTERED AT 14:38:15 ON 26 JUL 2005
               D QUE L21

     FILE 'MEDLINE' ENTERED AT 14:38:15 ON 26 JUL 2005
               D QUE L34

     FILE 'EMBASE' ENTERED AT 14:38:16 ON 26 JUL 2005
               D QUE L46
               D QUE L49
L75          11 SEA ABB=ON  L46 OR L49

     FILE 'PASCAL, BIOTECHNO, ESBIOBASE, BIOSIS, CONFSCI, BIOTECHDS, DISSABS,
     WPIDS' ENTERED AT 14:38:17 ON 26 JUL 2005
               D QUE L63
               D QUE L65
               D QUE L72
L76          32 SEA ABB=ON  L63 OR L65 OR L72
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FILE 'MEDLINE, CAPLUS, EMBASE, PASCAL, BIOTECHNO, ESBIOBASE, BIOSIS, WPIDS' ENTERED AT 14:38:36 ON 26 JUL 2005

L77 32 DUP REM L34 L21 L75 L76 (31 DUPLICATES REMOVED)
ANSWERS '1-9' FROM FILE MEDLINE
ANSWERS '10-20' FROM FILE CAPLUS
ANSWERS '21-25' FROM FILE EMBASE
ANSWERS '26-30' FROM FILE BIOTECHNO
ANSWERS '31-32' FROM FILE ESBIOBASE

D IALL 1-9
D IBIB ED ABS HITIND 10-20
D IALL 21-32

FILE 'HOME' ENTERED AT 14:39:10 ON 26 JUL 2005

FILE HOME

FILE CAPLUS

FILE COVERS 1907 - 26 Jul 2005 VOL 143 ISS 5
FILE LAST UPDATED: 25 Jul 2005 (20050725/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 25 JUL 2005 HIGHEST RN 856925-80-9
DICTIONARY FILE UPDATES: 25 JUL 2005 HIGHEST RN 856925-80-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

FILE MEDLINE
FILE LAST UPDATED: 23 JUL 2005 (20050723/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 21 Jul 2005 (20050721/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 22, 2005 (20050722/UP).

FILE PASCAL
FILE LAST UPDATED: 25 JUL 2005 <20050725/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE BASIC INDEX (/BI) FIELD <<<

FILE BIOTECHNO
FILE LAST UPDATED: 7 JAN 2004 <20040107/UP>
FILE COVERS 1980 TO 2003.

>>> BIOTECHNO IS NO LONGER BEING UPDATED AS OF 2004 <<<

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN /CT AND BASIC INDEX <<<

FILE ESBIOBASE
FILE LAST UPDATED: 26 JUL 2005 <20050726/UP>
FILE COVERS 1994 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
/CC, /ORGN, AND /ST <<<

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 21 July 2005 (20050721/ED)

FILE RELOADED: 19 October 2003.

FILE CONFSCI
FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

FILE BIOTECHDS
FILE LAST UPDATED: 20 JUL 2005 <20050720/UP>

>>> USE OF THIS FILE IS LIMITED TO BIOTECH SUBSCRIBERS <<<

>>> NEW CLASSIFICATION SYSTEM FROM 2002 ONWARDS - SEE HELP CLA <<<

>>> NEW DISPLAY FIELDS LS AND LS2 (LEGAL STATUS DATA FROM
THE INPADOC DATABASE) AVAILABLE - SEE NEWS <<<

FILE DISSABS
FILE COVERS 1861 TO 28 JUN 2005 (20050628/ED)

FILE WPIDS
FILE LAST UPDATED: 25 JUL 2005 <20050725/UP>
MOST RECENT DERWENT UPDATE: 200547 <200547/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://thomsonderwent.com/coverage/latestupdates/ <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
GUIDES, PLEASE VISIT:
http://thomsonderwent.com/support/userguides/ <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
PLEASE CHECK:

http://thomsonderwent.com/support/dwpiref/reftools/classification/code-rev
FOR DETAILS. <<<

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